US009266836B2

(12) **United States Patent**
Duncan et al.

(10) **Patent No.: US 9,266,836 B2**
(45) **Date of Patent: Feb. 23, 2016**

(54) **PRMT5 INHIBITORS AND USES THEREOF**

(71) Applicant: **Epizyme, Inc.**, Cambridge, MA (US)

(72) Inventors: **Kenneth W. Duncan**, Westwood, MA (US); **Richard Chesworth**, Concord, MA (US); **Paula Ann Boriack-Sjodin**, Lexington, MA (US); **Michael John Munchhof**, Salem, CT (US); **Lei Jin**, Wellesley, MA (US)

(73) Assignee: **Epizyme, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/561,538**

(22) Filed: **Dec. 5, 2014**

(65) **Prior Publication Data**

US 2015/0191432 A1 Jul. 9, 2015

Related U.S. Application Data

(63) Continuation of application No. 14/136,738, filed on Dec. 20, 2013, now Pat. No. 8,940,726.

(60) Provisional application No. 61/790,928, filed on Mar. 15, 2013, provisional application No. 61/745,490, filed on Dec. 21, 2012.

(51) **Int. Cl.**

C07D 217/00	(2006.01)
C07D 217/04	(2006.01)
C07D 401/14	(2006.01)
C07D 405/14	(2006.01)
C07D 217/16	(2006.01)
C07D 401/12	(2006.01)
C07D 405/12	(2006.01)
C07D 413/12	(2006.01)
C07D 417/12	(2006.01)
A61K 31/472	(2006.01)
A61K 31/4725	(2006.01)
A61K 31/497	(2006.01)
A61K 31/498	(2006.01)
A61K 31/502	(2006.01)
A61K 31/517	(2006.01)
A61K 31/5377	(2006.01)
A61K 31/538	(2006.01)

(52) **U.S. Cl.**

CPC ***C07D 217/04*** (2013.01); ***A61K 31/472*** (2013.01); ***A61K 31/4725*** (2013.01); ***A61K 31/497*** (2013.01); ***A61K 31/498*** (2013.01); ***A61K 31/502*** (2013.01); ***A61K 31/517*** (2013.01); ***A61K 31/538*** (2013.01); ***A61K 31/5377*** (2013.01); ***C07D 217/16*** (2013.01); ***C07D 401/12*** (2013.01); ***C07D 401/14*** (2013.01); ***C07D 405/12*** (2013.01); ***C07D 405/14*** (2013.01); ***C07D 413/12*** (2013.01); ***C07D 417/12*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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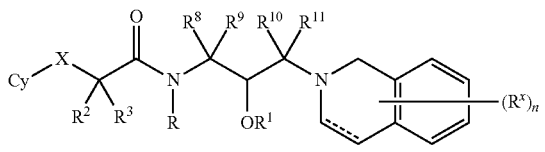
Primary Examiner — Heidi Reese

(74) *Attorney, Agent, or Firm* — Wolf, Greenfield & Sacks, P.C.

(57) **ABSTRACT**

Described herein are compounds of Formula (I), pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof. Compounds of the present invention are useful for inhibiting PRMT5 activity. Methods of using the compounds for treating PRMT5-mediated disorders are also described.

I



28 Claims, No Drawings

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PRMT5 INHIBITORS AND USES THEREOF

RELATED APPLICATIONS

This application is a continuation of and claims priority under 35 U.S.C. §120 to U.S. patent application Ser. No. 14/136,738, filed Dec. 20, 2013, now U.S. Pat. No. 8,940,726, which claims priority under 35 U.S.C. §119(e) to U.S. provisional patent application, U.S. Ser. No. 61/790,928, filed Mar. 15, 2013, and to U.S. provisional patent application, U.S. Ser. No. 61/745,490, filed Dec. 21, 2012, the entire contents of each of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Epigenetic regulation of gene expression is an important biological determinant of protein production and cellular differentiation and plays a significant pathogenic role in a number of human diseases.

Epigenetic regulation involves heritable modification of genetic material without changing its nucleotide sequence. Typically, epigenetic regulation is mediated by selective and reversible modification (e.g., methylation) of DNA and proteins (e.g., histones) that control the conformational transition between transcriptionally active and inactive states of chromatin. These covalent modifications can be controlled by enzymes such as methyltransferases (e.g., PRMT5), many of which are associated with specific genetic alterations that can cause human disease.

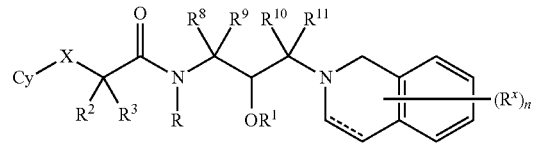
Disease-associated chromatin-modifying enzymes (e.g., PRMT5) play a role in diseases such as proliferative disorders, metabolic disorders, and blood disorders. Thus, there is a need for the development of small molecules that are capable of inhibiting the activity of PRMT5.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

Protein arginine methyltransferase 5 (PRMT5) catalyzes the addition of two methyl groups to the two ω-guanidino nitrogen atoms of arginine, resulting in ω-NG, N'G symmetric dimethylation of arginine (sDMA) of the target protein. PRMT5 functions in the nucleus as well as in the cytoplasm, and its substrates include histones, spliceosomal proteins, transcription factors (See e.g., Sun et al., 20011, PNAS 108: 20538-20543). PRMT5 generally functions as part of a molecule weight protein complex. While the protein complexes of PRMT5 can have a variety of components, they generally include the protein MEP50 (methylosome protein 50). In addition, PRMT5 acts in conjunction with cofactor SAM (S-adenosyl methionine).

PRMT5 is an attractive target for modulation given its role in the regulation of diverse biological processes. It has now been found that compounds described herein, and pharmaceutically acceptable salts and compositions thereof, are effective as inhibitors of PRMT5. Such compounds have the general Formula (I):

I



or a pharmaceutically acceptable salt thereof, wherein R, R^1, R^2, R^3, R^8, R^9, R^{10}, R^{11}, R^x, n, X, and Cy are as defined herein.

In some embodiments, pharmaceutical compositions are provided which comprise a compound described herein (e.g., a compound of Formula (I)), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

In certain embodiments, compounds described herein inhibit activity of PRMT5. In certain embodiments, methods of inhibiting PRMT5 are provided which comprise contacting PRMT5 with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. The PRMT5 may be purified or crude, and may be present in a cell, tissue, or a subject. Thus, such methods encompass inhibition of PRMT5 activity both in vitro and in vivo. In certain embodiments, the PRMT5 is wild-type PRMT5. In certain embodiments, the PRMT5 is overexpressed. In certain embodiments, the PRMT5 is a mutant. In certain embodiments, the PRMT5 is in a cell. In certain embodiments, the PRMT5 is in an animal, e.g., a human. In some embodiments, the PRMT5 is in a subject that is susceptible to normal levels of PRMT5 activity due to one or more mutations associated with a PRMT5 substrate. In some embodiments, the PRMT5 is in a subject known or identified as having abnormal PRMT5 activity (e.g., overexpression). In some embodiments, a provided compound is selective for PRMT5 over other methyltransferases. In certain embodiments, a provided compound is at least about 10-fold selective, at least about 20-fold selective, at least about 30-fold selective, at least about 40-fold selective, at least about 50-fold selective, at least about 60-fold selective, at least about 70-fold selective, at least about 80-fold selective, at least about 90-fold selective, or at least about 100-fold selective relative to one or more other methyltransferases.

In certain embodiments, methods of altering gene expression in a cell are provided which comprise contacting a cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the cell in culture in vitro. In certain embodiments, cell is in an animal, e.g., a human.

In certain embodiments, methods of altering transcription in a cell are provided which comprise contacting a cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the cell in culture in vitro. In certain embodiments, the cell is in an animal, e.g., a human.

In some embodiments, methods of treating a PRMT5-mediated disorder are provided which comprise administering to a subject suffering from a PRMT5-mediated disorder an effective amount of a compound described herein (e.g., a compound of Formula (I)), or a pharmaceutically acceptable

salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the PRMT5-mediated disorder is a proliferative disorder, a metabolic disorder, or a blood disorder. In certain embodiments, compounds described herein are useful for treating cancer. In certain embodiments, compounds described herein are useful for treating hematopoietic cancer, lung cancer, prostate cancer, melanoma, or pancreatic cancer. In certain embodiments, compounds described herein are useful for treating a hemoglobinopathy. In certain embodiments, compounds described herein are useful for treating sickle cell anemia. In certain embodiments, compounds described herein are useful for treating diabetes or obesity.

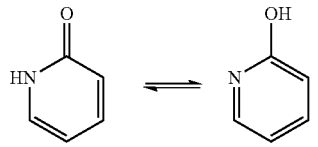
Compounds described herein are also useful for the study of PRMT5 in biological and pathological phenomena, the study of intracellular signal transduction pathways mediated by PRMT5, and the comparative evaluation of new PRMT5 inhibitors.

This application refers to various issued patent, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference.

Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics,* 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry,* 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis,* 3rd Edition, Cambridge University Press, Cambridge, 1987.

Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, e.g., enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques et al., *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen et al., *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E. L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, Ind. 1972). The present disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

It is to be understood that the compounds of the present invention may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present invention, and the naming of any compound described herein does not exclude any tautomer form.



pyridin-2(1H)-one pyridin-2-ol

Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, replacement of ^{19}F with ^{18}F, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of the disclosure. Such compounds are useful, for example, as analytical tools or probes in biological assays.

The term "aliphatic," as used herein, includes both saturated and unsaturated, nonaromatic, straight chain (i.e., unbranched), branched, acyclic, and cyclic (i.e., carbocyclic) hydrocarbons. In some embodiments, an aliphatic group is optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, "aliphatic" is intended herein to include alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl moieties.

When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

"Alkyl" refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms ("C_{1-20} alkyl"). In some embodiments, an alkyl group has 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), n-propyl (C_3), isopropyl (C_3), n-butyl (C_4), tert-butyl (C_4), sec-butyl (C_4), iso-butyl (C_4), n-pentyl (C_5), 3-pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3-methyl-2-butanyl (C_5), tertiary amyl (C_5), and n-hexyl (C_6). Additional examples of alkyl groups include n-heptyl (C_7), n-octyl (C_8) and the like. In certain embodiments, each instance of an alkyl group is independently optionally substituted, e.g., unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents. In certain embodiments, the alkyl group is unsubstituted C_{1-10} alkyl (e.g., —CH_3). In certain embodiments, the alkyl group is substituted C_{1-10} alkyl.

In some embodiments, an alkyl group is substituted with one or more halogens. "Perhaloalkyl" is a substituted alkyl group as defined herein wherein all of the hydrogen atoms are independently replaced by a halogen, e.g., fluoro, bromo, chloro, or iodo. In some embodiments, the alkyl moiety has 1 to 8 carbon atoms ("C_{1-8} perhaloalkyl"). In some embodi-

ments, the alkyl moiety has 1 to 6 carbon atoms ("C_{1-6} perhaloalkyl"). In some embodiments, the alkyl moiety has 1 to 4 carbon atoms ("C_1 perhaloalkyl"). In some embodiments, the alkyl moiety has 1 to 3 carbon atoms ("C_{1-3} perhaloalkyl"). In some embodiments, the alkyl moiety has 1 to 2 carbon atoms ("C_{1-2} perhaloalkyl"). In some embodiments, all of the hydrogen atoms are replaced with fluoro. In some embodiments, all of the hydrogen atoms are replaced with chloro. Examples of perhaloalkyl groups include —CF_3, —CF_2CF_3, —$CF_2CF_2CF_3$, —CCl_3, —$CFCl_2$, —CF_2Cl, and the like.

"Alkenyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon double bonds, and no triple bonds ("C_{2-20} alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C_{2-10} alkenyl"). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("C_{2-9} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("C_{2-7} alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6} alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. In certain embodiments, each instance of an alkenyl group is independently optionally substituted, e.g., unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is substituted C_{2-10} alkenyl.

"Alkynyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon triple bonds, and optionally one or more double bonds ("C_{2-20} alkynyl"). In some embodiments, an alkynyl group has 2 to 10 carbon atoms ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon-carbon triple bonds can be internal (such as in 2-butynyl) or terminal (such as in 1-butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. In certain embodiments, each instance of an alkynyl group is independently optionally substituted, e.g., unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is substituted C_{2-10} alkynyl.

"Carbocyclyl" or "carbocyclic" refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl") and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1H-indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") and can be saturated or can be partially unsaturated. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. In certain embodiments, each instance of a carbocyclyl group is independently optionally substituted, e.g., unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C_{3-10} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-10} carbocyclyl.

In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). In certain embodiments, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C_{3-10} cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C_{3-10} cycloalkyl.

"Heterocyclyl" or "heterocyclic" refers to a radical of a 3- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3-10 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. In certain embodiments, each instance of heterocyclyl is independently optionally substituted, e.g., unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3-10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3-10 membered heterocyclyl.

In some embodiments, a heterocyclyl group is a 5-10 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-8 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-6 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heterocyclyl"). In some embodiments, the 5-6 membered heterocyclyl has 1-3 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1-2 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, and thiorenyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl, and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C_6 aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

"Aryl" refers to a radical of a monocyclic or polycyclic (e.g., bicyclic or tricyclic) 4n+2 aromatic ring system (e.g., having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; e.g., phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; e.g., naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; e.g., anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. In certain embodiments, each instance of an aryl group is independently optionally substituted, e.g., unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is substituted C_{6-14} aryl.

"Heteroaryl" refers to a radical of a 5-10 membered monocyclic or bicyclic 4n+2 aromatic ring system (e.g., having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5-10 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (e.g., indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, e.g., either the ring bearing a heteroatom (e.g., 2-indolyl) or the ring that does not contain a heteroatom (e.g., 5-indolyl).

In some embodiments, a heteroaryl group is a 5-10 membered aromatic ring system having ring carbon atoms and 1-4

ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-8 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heteroaryl"). In some embodiments, the 5-6 membered heteroaryl has 1-3 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1-2 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, each instance of a heteroaryl group is independently optionally substituted, e.g., unsubstituted ("unsubstituted heteroaryl") or substituted ("substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5-14 membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5-14 membered heteroaryl.

Exemplary 5-membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

"Partially unsaturated" refers to a group that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic groups (e.g., aryl or heteroaryl groups) as herein defined. Likewise, "saturated" refers to a group that does not contain a double or triple bond, i.e., contains all single bonds.

In some embodiments, aliphatic, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are optionally substituted (e.g., "substituted" or "unsubstituted" aliphatic, "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (e.g., a carbon or nitrogen atom) is replaced with a permissible substituent, e.g., a substituent which upon substitution results in a stable compound, e.g., a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, including any of the substituents described herein that results in the formation of a stable compound. The present disclosure contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this disclosure, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

Exemplary carbon atom substituents include, but are not limited to, halogen, —CN, —NO_2, —N_3, —SO_2H, —SO_3H, —OH, —OR^{aa}, —$ON(R^{bb})_2$, —$N(R^{bb})_2$, —$N(R^{bb})_3{}^+X^-$, —$N(OR^{cc})R^{bb}$, —SH, —SR^{aa}, —SSR^{cc}, —$C(=O)R^{aa}$, —CO_2H, —CHO, —$C(OR^{cc})_2$, —CO_2R^{aa}, —$OC(=O)R^{aa}$, —OCO_2R^{aa}, —$C(=O)N(R^{bb})_2$, —$OC(=O)N(R^{bb})_2$, —$NR^{bb}C(=O)R^{aa}$, —$NR^{bb}CO_2R^{aa}$, —$NR^{bb}C(=O)N(R^{bb})_2$, —$C(=NR^{bb})R^{aa}$, —$C(=NR^{bb})OR^{aa}$, —$OC(=NR^{bb})R^{aa}$, —$OC(=NR^{bb})OR^{aa}$, —$C(=NR^{bb})N(R^{bb})_2$, —$OC(=NR^{bb})N(R^{bb})_2$, —$NR^{bb}C(=NR^{bb})N(R^{bb})_2$, —$C(=O)NR^{bb}SO_2R^{aa}$, —$NR^{bb}SO_2R^{aa}$, —$SO_2N(R^{bb})_2$, —$SO_2R^{aa}$, —$SO_2OR^{aa}$, —$OSO_2R^{aa}$, —$S(=O)R^{aa}$, —$OS(=O)R^{aa}$, —$Si(R^{aa})_3$, —$OSi(R^{aa})_3$—$(=S)N(R^{bb})_2$, —$C(=O)SR^{aa}$, —$C(=S)SR^{aa}$, —$SC(=S)SR^{aa}$, —$SC(=O)SR^{aa}$, —$OC(=O)SR^{aa}$, —$SC(=O)OR^{aa}$, —$SC(=O)R^{aa}$, —$P(=O)_2R^{aa}$, —$OP(=O)_2R^{aa}$, —$P(=O)(R^{aa})_2$, —$OP(=O)(R^{aa})_2$, —$OP(=O)(OR^{cc})_2$, —$P(=O)_2N(R^{bb})_2$, —$OP(=O)_2N(R^{bb})_2$, —$P(=O)(NR^{bb})_2$, —$OP(=O)(NR^{bb})_2$, —$NR^{bb}P(=O)(OR^{cc})_2$, —$NR^{bb}P(=O)(NR^{bb})_2$, —$P(R^{cc})_2$, —$P(R^{cc})_3$, —$OP(R^{cc})_2$, —$OP(R^{cc})_3$, —$B(R^{aa})_2$, —$B(OR^{cc})_2$, —$BR^{aa}(OR^{cc})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{aa} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, —OH, —OR^{aa}, —$N(R^{cc})_2$, —CN, —$C(=O)R^{aa}$, —$C(=O)N(R^{cc})_2$, —CO_2R^{aa}, —SO_2R^{aa}, —$C(=NR^{cc})OR^{aa}$, —$C(=NR^{cc})N(R^{cc})_2$, —$SO_2N(R^{cc})_2$, —SO_2R^{cc}, —SO_2OR^{cc}, —SOR^{aa}, —$C(=S)N(R^{cc})_2$, —$C(=O)SR^{cc}$, —$C(=S)SR^{cc}$, —$P(=O)_2R^{aa}$, —$P(=O)(R^{aa})_2$, —P

$(=O)_2N(R^{cc})_2$, —$P(=O)(NR^{cc})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{bb} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, —CN, —NO_2, —N_3, —SO_2H, —SO_3H, —OH, —OR^{ee}, —$ON(R^{ff})_2$, —$N(R^{ff})_2$, —$N(R^{ff})_3{}^+X^-$, —$N(OR^{ee})R^{ff}$, —SH, —SR^{ee}, —SSR^{ee}, —$C(=O)R^{ee}$, —CO_2H, —CO_2R^{ee}, —$OC(=O)R^{ee}$, —OCO_2R^{ee}, —$C(=O)N(R^{ff})_2$, —$OC(=O)N(R^{ff})_2$, —$NR^{ff}C(=O)R^{ee}$, —$NR^{ff}CO_2R^{ee}$, —$NR^{ff}C(=O)N(R^{ff})_2$, —$C(=NR^{ff})OR^{ee}$, —$OC(=NR^{ff})R^{ee}$, —$OC(=NR^{ff})OR^{ee}$, —$C(=NR^{ff})N(R^{ff})_2$, —$OC(=NR^{ff})N(R^{ff})_2$, —$NR^{ff}C(=NR^{ff})N(R^{ff})_2$, —$NR^{ff}SO_2R^{ee}$, —$SO_2N(R^{ff})_2$, —$SO_2R^{ee}$, —$SO_2OR^{ee}$, —$OSO_2R^{ee}$, —$S(=O)R^{ee}$, —$Si(R^{ee})_3$, —$OSi(R^{ee})_3$, —$C(=S)N(R^{ff})_2$, —$C(=O)SR^{ee}$, —$C(=S)SR^{ee}$, —$SC(=S)SR^{ee}$, —$P(=O)_2R^{ee}$, —$P(=O)(R^{ee})_2$, —$OP(=O)(R^{ee})_2$, —$OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

each instance of R^{ee} is, independently, selected from C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl, or two R^{ff} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, —CN, —NO_2, —N_3, —SO_2H, —SO_3H, —OH, —OC_{1-6} alkyl, —$ON(C_{1-6}$ alkyl$)_2$, —$N(C_{1-6}$ alkyl$)_2$, —$N(C_{1-6}$ alkyl$)_3{}^+X^-$, —$NH(C_{1-6}$ alkyl$)_2{}^+X^-$, —$NH_2(C_{1-6}$ alkyl$)^+X^-$, —$NH_3{}^+X^-$, —$N(OC_{1-6}$ alkyl$)(C_{1-6}$ alkyl), —$N(OH)(C_{1-6}$ alkyl), —NH(OH), —SH, —SC_{1-6} alkyl, —$SS(C_{1-6}$ alkyl), —$C(=O)(C_{1-6}$ alkyl), —CO_2H, —$CO_2(C_{1-6}$ alkyl), —$OC(=O)(C_{1-6}$ alkyl), —$OCO_2(C_{1-6}$ alkyl), —$C(=O)NH_2$, —$C(=O)N(C_{1-6}$ alkyl$)_2$, —$OC(=O)NH(C_{1-6}$ alkyl), —$NHC(=O)(C_{1-6}$ alkyl), —$N(C_{1-6}$ alkyl$)C(=O)(C_{1-6}$ alkyl), —$NHCO_2(C_{1-6}$ alkyl), —$NHC(=O)N(C_{1-6}$ alkyl$)_2$, —$NHC(=O)NH(C_{1-6}$ alkyl), —$NHC(=O)NH_2$, —$C(=NH)O(C_{1-6}$ alkyl), —$OC(=NH)(C_{1-6}$ alkyl), —$OC(=NH)OC_{1-6}$ alkyl, —$C(=NH)N(C_{1-6}$ alkyl$)_2$, —$C(=NH)NH(C_{1-6}$ alkyl), —$C(=NH)NH_2$, —$OC(=NH)N(C_{1-6}$ alkyl$)_2$, —$OC(NH)NH(C_{1-6}$ alkyl), —$OC(NH)NH_2$, —$NHC(NH)N(C_{1-6}$ alkyl$)_2$, —$NHC(=NH)NH_2$, —$NHSO_2(C_{1-6}$ alkyl), —$SO_2N(C_{1-6}$ alkyl$)_2$, —$SO_2NH(C_{1-6}$ alkyl), —SO_2NH_2, —SO_2C_{1-6} alkyl, —SO_2OC_{1-6} alkyl, —OSO_2C_{1-6} alkyl, —SOC_{1-6} alkyl, —$Si(C_{1-6}$ alkyl$)_3$, —$OSi(C_{1-6}$ alkyl$)_3$-$C(=S)N(C_{1-6}$ alkyl$)_2$, $C(=S)NH(C_{1-6}$ alkyl), $C(=S)NH_2$, —$C(=O)S(C_{1-6}$ alkyl), —$C(=S)SC_{1-6}$ alkyl, —$SC(=S)SC_{1-6}$ alkyl, —$P(=O)_2(C_{1-6}$ alkyl), —$P(=O)(C_{1-6}$ alkyl$)_2$, —$OP(=O)(C_{1-6}$ alkyl$)_2$, —$OP(=O)(OC_{1-6}$ alkyl$)_2$, C_1 alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein X^- is a counterion.

A "counterion" or "anionic counterion" is a negatively charged group associated with a cationic quaternary amino group in order to maintain electronic neutrality. Exemplary counterions include halide ions (e.g., F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HSO_4^-, sulfonate ions (e.g., methansulfonate, trifluoromethanesulfonate, p-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate, naphthalene-1-sulfonic acid-5-sulfonate, ethan-1-sulfonic acid-2-sulfonate, and the like), and carboxylate ions (e.g., acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

"Halo" or "halogen" refers to fluorine (fluoro, —F), chlorine (chloro, —Cl), bromine (bromo, —Br), or iodine (iodo, —I).

Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom substitutents include, but are not limited to, hydrogen, —OH, —OR^{aa}, —$N(R^{cc})_2$, —CN, —$C(=O)R^{aa}$, —$C(=O)N(R^{cc})_2$, —CO_2R^{aa}, —SO_2R^{aa}, —$C(=NR^{bb})R^{aa}$, —$C(=NR^{cc})OR^{aa}$, —$C(=NR^{cc})N(R^{cc})_2$, —$SO_2N(R^{cc})_2$, —SO_2R^{cc}, —SO_2OR^{cc}, —SOR^{aa}, —$C(=S)N(R^{cc})_2$, —$C(=O)SR^{cc}$, —$C(=S)SR^{cc}$, —$P(=O)_2R^{aa}$, —$P(=O)(R^{aa})_2$, —$P(=O)_2N(R^{cc})_2$, —$P(=O)(NR^{cc})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups include, but are not limited to, —OH, —OR^{aa}, —$N(R^{cc})_2$, —$C(=O)R^{aa}$, —$C(=O)N(R^{cc})_2$, —CO_2R^{aa}, —SO_2R^{aa}, —$C(=NR^{cc})R^{aa}$, —$C(=NR^{cc})OR^{aa}$, —$C(=NR^{cc})N(R^{cc})_2$, —$SO_2N(R^{cc})_2$, —SO_2R^{cc}, —SO_2OR^{cc}, —SOR^{aa}, —$C(=S)N(R^{cc})_2$, —$C(=O)SR^{cc}$, —$C(=S)SR^{cc}$, C_{1-10} alkyl (e.g., aralkyl, heteroaralkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc}, and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

Amide nitrogen protecting groups (e.g., —$C(=O)R^{aa}$) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, N-benzoylphenylalanyl derivative, benzamide, p-phenylbenzamide, o-nitophenylacetamide, o-nitrophenoxyacetamide, acetoacetamide, (N'-dithiobenzyloxyacy-

lamino)acetamide, 3-(p-hydroxyphenyl)propanamide, 3-(o-nitrophenyl)propanamide, 2-methyl-2-(o-nitrophenoxy) propanamide, 2-methyl-2-(o-phenylazophenoxy) propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, o-nitrocinnamide, N-acetylmethionine, o-nitrobenzamide, and o-(benzoyloxymethyl)benzamide.

Carbamate nitrogen protecting groups (e.g., —C(═O)OR^{aa}) include, but are not limited to, methyl carbamate, ethyl carbamante, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluoroenylmethyl carbamate, 2,7-di-t-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamantyl)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-t-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenylyl)ethyl carbamate (Bpoc), 1-(3,5-di-t-butylphenyl)-1-methylethyl carbamate (t-Bumeoc), 2-(2'- and 4'-pyridyl)ethyl carbamate (Pyoc), 2-(N,N-dicyclohexylcarboxamido)ethyl carbamate, t-butyl carbamate (BOC), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, N-hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), p-methoxybenzyl carbamate (Moz), p-nitobenzyl carbamate, p-bromobenzyl carbamate, p-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (Msz), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonylethyl carbamate, 2-(p-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, m-chloro-p-acyloxybenzyl carbamate, p-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Tcroc), m-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, o-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(o-nitrophenyl)methyl carbamate, t-amyl carbamate, S-benzyl thiocarbamate, p-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, p-decyloxybenzyl carbamate, 2,2-dimethoxyacylvinyl carbamate, o-(N,N-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(N,N-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isobornyl carbamate, isobutyl carbamate, isonicotinyl carbamate, p-(p'-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(p-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, p-(phenylazo)benzyl carbamate, 2,4,6-tri-t-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

Sulfonamide nitrogen protecting groups (e.g., —S(═O)$_2R^{aa}$) include, but are not limited to, p-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β-trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

Other nitrogen protecting groups include, but are not limited to, phenothiazinyl-(10)-acyl derivative, N'-p-toluenesulfonylaminoacyl derivative, N'-phenylaminothioacyl derivative, N-benzoylphenylalanyl derivative, N-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, N-phthalimide, N-dithiasuccinimide (Dts), N-2,3-diphenylmaleimide, N-2,5-dimethylpyrrole, N-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, N-methylamine, N-allylamine, N-[2-(trimethylsilyl)ethoxy]methylamine (SEM), N-3-acetoxypropylamine, N-(1-isopropyl-4-nitro-2-oxo-3-pyroolin-3-yl)amine, quaternary ammonium salts, N-benzylamine, N-di(4-methoxyphenyl)methylamine, N-5-dibenzosuberylamine, N-triphenylmethylamine (Tr), N-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), N-9-phenylfluorenylamine (PhF), N-2,7-dichloro-9-fluorenylmethyleneamine, N-ferrocenylmethylamino (Fcm), N-2-picolylamino N'-oxide, N-1,1-dimethylthiomethyleneamine, N-benzylideneamine, N-p-methoxybenzylideneamine, N-diphenylmethyleneamine, N-[(2-pyridyl)mesityl]methyleneamine, N—(N',N'-dimethylaminomethylene)amine, N,N'-isopropylidenediamine, N-p-nitrobenzylideneamine, N-salicylideneamine, N-5-chlorosalicylideneamine, N-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, N-cyclohexylideneamine, N-(5,5-dimethyl-3-oxo-1-cyclohexenyl) amine, N-borane derivative, N-diphenylborinic acid derivative, N-[phenyl(pentaacylchromium- or tungsten)acyl] amine, N-copper chelate, N-zinc chelate, N-nitroamine, N-nitrosoamine, amine N-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, o-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys).

In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups include, but are not limited to, —R^{aa}, —$N(R^{bb})_2$, —C(═O)SR^{aa}, —C(═O)R^{aa}, —CO_2R^{aa}, —C(═O)$N(R^{bb})_2$, —C(═NR^{bb})R^{aa}, —C(═NR^{bb})OR^{aa}, —C(═NR^{bb})$N(R^{bb})_2$, —S(═O)R^{aa}, —SO_2R^{aa}, —$Si(R^{aa})_3$, —$P(R^{cc})_2$, —$P(R^{cc})_3$, —$P(═O)_2R^{aa}$, —$P(═O)(R^{aa})_2$, —P(═O)$(OR^{cc})_2$, —$P(═O)_2N(R^{bb})_2$, and —$P(═O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), t-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), p-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (p-AOM), guaiacolmethyl (GUM), t-butoxymethyl, 4-pente-

nyloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy) ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, t-butyl, allyl, p-chlorophenyl, p-methoxyphenyl, 2,4-dinitrophenyl, benzyl (Bn), p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, p-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl N-oxido, diphenylmethyl, p,p'-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α-naphthyldiphenylmethyl, p-methoxyphenyldiphenylmethyl, di(p-methoxyphenyl)phenylmethyl, tri(p-methoxyphenyl)methyl, 4-(4'-bromophenacyloxyphenyl)diphenylmethyl, 4,4',4"-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-tris(levulinoyloxyphenyl)methyl, 4,4',4"-tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-yl)bis(4',4"-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodisulfuran-2-yl, benzisothiazolyl S,S-dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, t-butyldimethylsilyl (TBDMS), t-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), t-butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, p-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, p-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), alkyl methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl)ethyl carbonate (Psec), 2-(triphenylphosphonio)ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate alkyl allyl carbonate, alkyl p-nitrophenyl carbonate, alkyl benzyl carbonate, alkyl p-methoxybenzyl carbonate, alkyl 3,4-dimethoxybenzyl carbonate, alkyl o-nitrobenzyl carbonate, alkyl p-nitrobenzyl carbonate, alkyl S-benzyl thiocarbonate, 4-ethoxy-1-napththyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, o-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (E)-2-methyl-2-butenoate, o-(methoxyacyl)benzoate, α-naphthoate, nitrate, alkyl N,N,N',N'-tetramethylphosphorodiamidate, alkyl N-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a thiol protecting group). Sulfur protecting groups include, but are not limited to, $—R^{aa}$, $—N(R^{bb})_2$, $—C(=O)SR^{aa}$, $—C(=O)R^{aa}$, $—CO_2R^{aa}$, $—C(=O)N(R^{bb})_2$, $—C(=NR^{bb})R^{aa}$, $—C(=NR^{bb})OR^{aa}$, $—C(=NR^{bb})N(R^{bb})_2$, $—S(=O)R^{aa}$, $—SO_2R^{aa}$, $—Si(R^{aa})_3$, $—P(R^{cc})_2$, $—P(R^{cc})_3$, $—P(O)_2R^{aa}$, $—P(O)(R^{aa})_2$, $—P(=O)(OR^{cc})_2$, $—P(=O)_2N(R^{bb})_2$, and $—P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and claims. The present disclosure is not intended to be limited in any manner by the above exemplary listing of substituents.

"Pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge et al. describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1-19. Pharmaceutically acceptable salts of the compounds describe herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxyethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, quaternary salts.

A "subject" to which administration is contemplated includes, but is not limited to, humans (e.g., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult or senior adult)) and/or other non-human animals, for example, non-human mammals (e.g., primates (e.g., cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs), birds (e.g., commercially relevant birds such as chickens, ducks, geese, and/or turkeys), rodents (e.g., rats and/or mice), reptiles, amphibians, and fish. In certain embodiments, the non-human animal is a mammal. The non-

human animal may be a male or female at any stage of development. A non-human animal may be a transgenic animal.

"Condition," "disease," and "disorder" are used interchangeably herein.

"Treat," "treating" and "treatment" encompasses an action that occurs while a subject is suffering from a condition which reduces the severity of the condition or retards or slows the progression of the condition ("therapeutic treatment"). "Treat," "treating" and "treatment" also encompasses an action that occurs before a subject begins to suffer from the condition and which inhibits or reduces the severity of the condition ("prophylactic treatment").

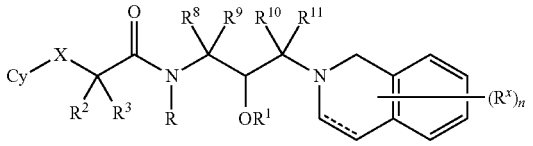
An "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response, e.g., treat the condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

A "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent.

A "prophylactically effective amount" of a compound is an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

As used herein, the term "methyltransferase" represents transferase class enzymes that are able to transfer a methyl group from a donor molecule to an acceptor molecule, e.g., an amino acid residue of a protein or a nucleic base of a DNA molecule. Methytransferases typically use a reactive methyl group bound to sulfur in S-adenosyl methionine (SAM) as the methyl donor. In some embodiments, a methyltransferase described herein is a protein methyltransferase. In some embodiments, a methyltransferase described herein is a histone methyltransferase. Histone methyltransferases (HMT) are histone-modifying enzymes, (including histone-lysine N-methyltransferase and histone-arginine N-methyltransferase), that catalyze the transfer of one or more methyl groups to lysine and arginine residues of histone proteins. In certain embodiments, a methyltransferase described herein is a histone-arginine N-methyltransferase.

As generally described above, provided herein are compounds useful as PRMT5 inhibitors. In some embodiments, the present disclosure provides a compound of Formula (I):



I

or a pharmaceutically acceptable salt thereof,

wherein

⋯⋯ represents a single or double bond;

R^1 is hydrogen, R^z, or —C(O)R^z, wherein R^z is optionally substituted C_{1-6} alkyl;

X is a bond, —O—, —N(R)—, —CR^4R^5—, —O—CR^4R^5, —N(R)—CR^4R^5—, —O—CR^4R^5—O—, —N(R)—CR^4R^5—O, —N(R)—CR^4R^5—N(R)—, —O—CR^4R^5—N(R)—, —CR^4R^5—O—, —CR^4R^5—N(R)—, —O—CR^4R^5—CR^6R^7—, —N(R)—CR^4R^5—CR^6R^7—, —CR^6R^7—CR^4R^5—O—, —CR^6R^7—CR^4R^5—N(R)—, or —CR^6R^7—CR^4R^5—;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

R^2 and R^3 are independently selected from the group consisting of hydrogen, halo, —CN, —NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)_2$, —SR^A, —C(=O)R^A, —C(O)OR^A, —C(O)SR^A, —C(O)$N(R^B)_2$, —C(O)$N(R^B)N(R^B)_2$, —OC(O)R^A, —OC(O)$N(R^B)_2$, —NR^BC(O)R^A, —NR^BC(O)$N(R^B)_2$, —NR^BC(O)$N(R^B)N(R^B)_2$, —NR^BC(O)OR^A, —SC(O)R^A, —C(=NR^B)R^A, —C(=NNR^B)R^A, —C(=NOR^A)R^A, —C(=NR^B)$N(R^B)_2$, —NR^BC(=NR^B)R^B, —C(=S)R^A, —C(=S)$N(R^B)_2$, —NR^BC(=S)R^A, —S(O)R^A, —$OS(O)_2R^A$, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$; or R^2 and R^3 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

R^4 and R^5 are independently selected from the group consisting of hydrogen, halo, —CN, —NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)_2$, —SR^A, —C(=O)R^A, —C(O)OR^A, —C(O)SR^A, —C(O)$N(R^B)_2$, —C(O)$N(R^B)N(R^B)_2$, —OC(O)R^A, —OC(O)$N(R^B)_2$, —NR^BC(O)R^A, —NR^BC(O)$N(R^B)_2$, —NR^BC(O)$N(R^B)N(R^B)_2$, —NR^BC(O)OR^A, —SC(O)R^A, —C(=NR^B)R^A, —C(=NNR^B)R^A, —C(=NOR^A)R^A, —C(=NR^B)$N(R^B)_2$, —NR^BC(=NR^B)R^B, —C(=S)R^A, —C(=S)$N(R^B)_2$, —NR^BC(=S)R^A, —S(O)R^A, —$OS(O)_2R^A$, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$; or R^4 and R^5 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

R^6 and R^7 are independently selected from the group consisting of hydrogen, halo, —CN, —NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)_2$, —SR^A, —C(=O)R^A, —C(O)OR^A, —C(O)SR^A, —C(O)$N(R^B)_2$, —C(O)$N(R^B)N(R^B)_2$, —OC(O)R^A, —OC(O)$N(R^B)_2$, —NR^BC(O)R^A, —NR^BC(O)$N(R^B)_2$, —NR^BC(O)$N(R^B)N(R^B)_2$, —NR^BC(O)OR^A, —SC(O)R^A, —C(=NR^B)R^A, —C(=NNR^B)R^A, —C(=NOR^A)R^A, —C(=NR^B)$N(R^B)_2$,

—$NR^BC(=NR^B)R^B$, —$C(=S)R^A$, —$C(=S)N(R^B)_2$, —$NR^BC(=S)R^A$, —$S(O)R^A$, —$OS(O)_2R^A$, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$; or R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

R^8, R^9, R^{10}, and R^{11} are independently hydrogen, halo, or optionally substituted aliphatic;

Cy is a monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with 0, 1, 2, 3, or 4 R^y groups;

each R^y is independently selected from the group consisting of halo, —CN, —NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)_2$, —SR^A, —$C(=O)R^A$, —$C(O)OR^A$, —$C(O)SR^A$, —$C(O)N(R^B)_2$, —$C(O)N(R^B)N(R^B)_2$, —$OC(O)R^A$, —$OC(O)N(R^B)_2$, —$NR^BC(O)R^A$, —$NR^BC(O)N(R^B)_2$, —$NR^BC(O)N(R^B)N(R^B)_2$, —$NR^BC(O)OR^A$, —$SC(O)R^A$, —$C(=NR^B)R^A$, —$C(=NNR^B)R^A$, —$C(=NOR^A)R^A$, —$C(=NR^B)N(R^B)_2$, —$NR^BC(=NR^B)R^B$, —$C(=S)R^A$, —$C(=S)N(R^B)_2$, —$NR^BC(=S)R^A$, —$S(O)R^A$, —$OS(O)_2R^A$, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$; or an R^y group may be optionally taken together with R^2 or R^3 to form an optionally substituted 5- to 6-membered carbocyclic or heterocyclic ring fused to Cy;

each R^x is independently selected from the group consisting of halo, —CN, optionally substituted aliphatic, —OR', and —$N(R'')_2$;

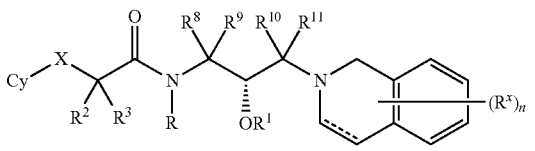
R' is hydrogen or optionally substituted aliphatic;

each R'' is independently hydrogen or optionally substituted aliphatic, or two R'' are taken together with their intervening atoms to form an optionally substituted heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits.

In certain embodiments, a provided compound is of Formula (I-a):

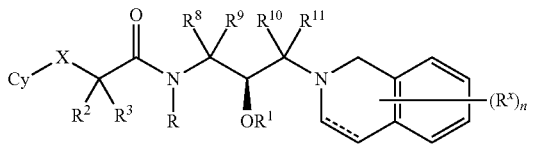
I-a



or a pharmaceutically acceptable salt thereof, wherein R, R^1, R^2, R^3, R^8, R^9, R^{10}, R^{11}, R^x, n, X, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (I-b):

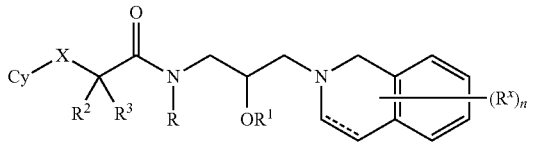
I-b



or a pharmaceutically acceptable salt thereof, wherein R, R^1, R^2, R^3, R^8, R^9, R^{10}, R^{11}, R^x, n, X, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (I-c):

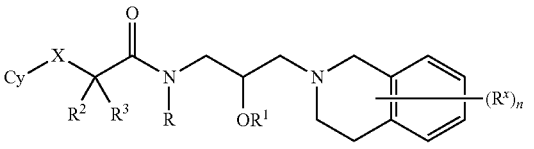
I-c



or a pharmaceutically acceptable salt thereof, wherein R, R^1, R^2, R^3, R^x, n, X, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (I'):

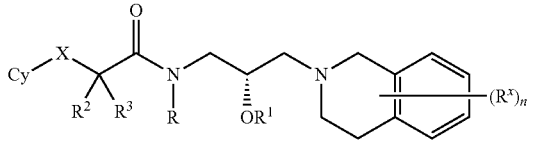
I'



or a pharmaceutically acceptable salt thereof, wherein R, R^1, R^2, R^3, R^x, n, X, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (I'-a):

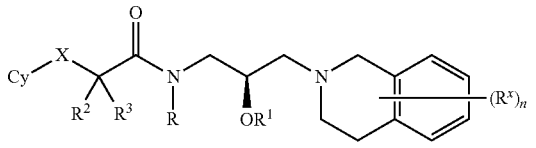
I'-a



or a pharmaceutically acceptable salt thereof, wherein R, R^1, R^2, R^3, R^x, n, X, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (I'-b):

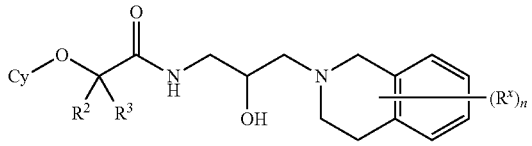
I′-b



or a pharmaceutically acceptable salt thereof, wherein R, R^1, R^2, R^3, R^x, n, X, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (II):

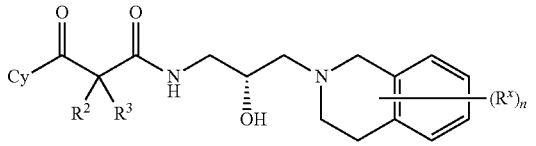
II



or a pharmaceutically acceptable salt thereof, wherein R^2, R^3, R^x, n, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (II-a):

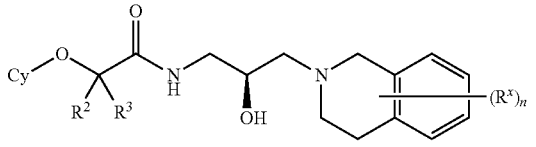
II-a



or a pharmaceutically acceptable salt thereof, wherein R^2, R^3, R^x, n, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (II-b):

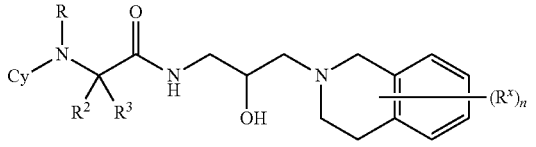
II-b



or a pharmaceutically acceptable salt thereof, wherein R^2, R^3, R^x, n, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (III):

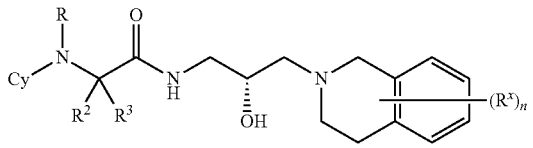
III



or a pharmaceutically acceptable salt thereof, wherein R, R^2, R^3, R^x, n, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (III-a):

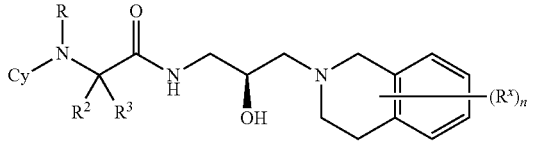
III-a



or a pharmaceutically acceptable salt thereof, wherein R, R^2, R^3, R^x, n, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (III-b):

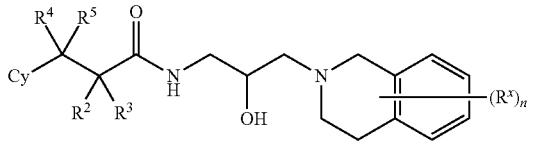
III-b



or a pharmaceutically acceptable salt thereof, wherein R, R^2, R^3, R^x, n, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (IV):

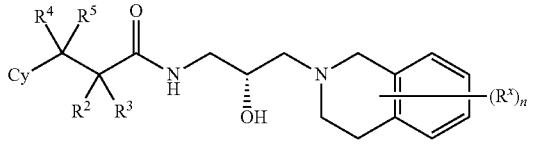
IV



or a pharmaceutically acceptable salt thereof, wherein R^2, R^3, R^4, R^5, R^x, n, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (IV-a):

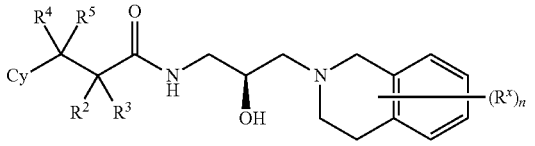
IV-a



or a pharmaceutically acceptable salt thereof, wherein R^2, R^3, R^4, R^5, R^x, n, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (IV-b):

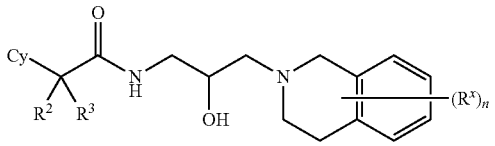
IV-b



or a pharmaceutically acceptable salt thereof, wherein R^2, R^3, R^4, R^5, R^x, n, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (V):

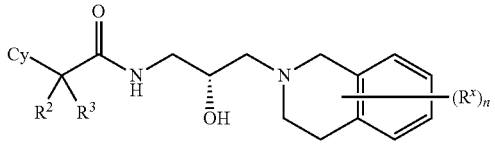
V



or a pharmaceutically acceptable salt thereof, wherein R^2, R^3, R^x, n, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (V-a):

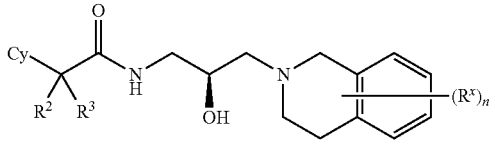
V-a



or a pharmaceutically acceptable salt thereof, wherein R^2, R^3, R^x, n, and Cy are as described herein.

In certain embodiments, a provided compound is of Formula (V-b):

V-b



or a pharmaceutically acceptable salt thereof, wherein R^2, R^3, R^x, n, and Cy are as described herein.

In some embodiments, ⁼⁼⁼⁼⁼ represents a single bond. In some embodiments, ⁼⁼⁼⁼⁼ represents a double bond.

As defined generally above, R^1 is hydrogen, R^z, or —C(O)R^z, wherein R^z is optionally substituted C_{1-6} alkyl. In certain embodiments, R^1 is hydrogen. In some embodiments, R^1 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^1 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^1 is methyl, ethyl, or propyl. In some embodiments, R^1 is —C(O)R^z, wherein R^z is optionally substituted C_{1-6} alkyl. In certain embodiments, R^1 is —C(O)R^z, wherein R^z is unsubstituted C_{1-6} alkyl. In certain embodiments, R^1 is acetyl.

As defined generally above, X is a bond, —O—, —N(R)—, —CR^4R^5—, —O—CR^4R^5, —N(R)—CR^4R^5—, —O—CR^4R^5—O—, —N(R)—CR^4R^5—O, —N(R)—CR^4R^5—N(R)—, —O—CR^4R^5—N(R)—, —CR^4R^5—O—, —CR^4R^5—N(R)—, —O—CR^4R^5—CR^6R^7—, —N(R)—CR^4R^5—CR^6R^7—, —CR^6R^7—CR^4R^5—O—, —CR^6R^7—CR^4R^5—N(R)—, or —CR^6R^7—CR^4R^5—. In certain embodiments, X is a bond, —O—, —N(R)—, or —CR^4R^5—, wherein R, R^4, and R^5 are as described herein. In certain embodiments, X is a bond. In certain embodiments, X is —O—. In some embodiments, X is —N(R)—. In certain embodiments, X is —NH—. In certain embodiments, X is —N(R)—, wherein R is optionally substituted C_{1-6} aliphatic. In certain embodiments, X is —N(R)—, wherein R is optionally substituted C_{1-6} alkyl. In certain embodiments, X is —N(R)—, wherein R is unsubstituted C_{1-6} alkyl. In certain embodiments, X is —N(Me)-. In some embodiments, X is —CR^4R^5—. In certain embodiments, X is —CH_2—. In certain embodiments, X is —CH_2—O—.

As defined generally above, each R is independently hydrogen or optionally substituted C_{1-6} aliphatic. In certain embodiments, R is hydrogen. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is substituted C_{1-6} aliphatic. In some embodiments, R is unsubstituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is substituted C_{1-6} alkyl. In some embodiments, R is unsubstituted C_{1-6} alkyl. In some embodiments, R is methyl, ethyl, or propyl.

As defined generally above, R^2 and R^3 are independently selected from the group consisting of hydrogen, halo, —CN, —NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)_2$, —SR^A, —C(=O)R^A, —C(O)OR^A, —C(O)SR^A, —C(O)$N(R^B)_2$, —C(O)$N(R^B)N(R^B)_2$, —OC(O)R^A, —OC(O)$N(R^B)_2$, —NR^BC(O)R^A, —NR^BC(O)$N(R^B)_2$, —NR^BC(O)$N(R^B)N(R^B)_2$, —NR^BC(O)OR^A, —SC(O)R^A, —C(=NR^B)R^A, —C(=NNR^B)R^A, —C(=NOR^A)R^A, —C(=NR^B)$N(R^B)_2$, —NR^BC(=NR^B)R^B, —C(=S)R^A, —C(=S)$N(R^B)_2$, —NR^BC(=S)R^A, —S(O)R^A, —OS(O)$_2R^A$, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$; or R^2 and R^3 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring. In certain embodiments, R^2 and R^3 are independently selected from the group consisting of hydrogen, halo, —CN, —NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)_2$, —SR^A, —C(=O)R^A, —C(O)OR^A, —C(O)SR^A, —C(O)$N(R^B)_2$, —OC(O)R^A, —NR^BC(O)R^A, —NR^BC(O)$N(R^B)_2$, —SC(O)R^A, —C(=NR^B)R^A, —C(=NR^B)$N(R^B)_2$, —NR^BC(=NR^B)R^B, —C(=S)R^A, —C(=S)$N(R^B)_2$, —NR^BC(=S)R^A, —S(O)R^A, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$; or R^2 and R^3 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring.

In certain embodiments, R^2 is hydrogen. In some embodiments, R^2 is not hydrogen. In some embodiments, R^2 is halo. In certain embodiments, R^2 is fluoro. In some embodiments, R^2 is optionally substituted aliphatic. In certain embodiments, R^2 is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^2 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^2 is substituted C_{1-6} alkyl. In certain embodiments, R^2 is —CF_3, CHF_2, or CH_2F. In certain embodiments, R^2 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^2 is methyl, ethyl, or propyl. In some embodiments, R^2 is —CN or —NO_2. In some embodiments, R^2 is optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, or optionally

substituted heteroaryl. In some embodiments, R^2 is —OR^A, —$N(R^B)_2$, —SR^A, —$C(=O)R^A$, —$C(O)OR^A$, —$C(O)SR^A$, —$C(O)N(R^B)_2$, —$OC(O)R^A$, —$NR^BC(O)R^A$, —$NR^BC(O)N(R^B)_2$, —$SC(O)R^A$, —$C(=NR^B)R^A$, —$C(=NR^B)N(R^B)_2$, —$NR^BC(=NR^B)R^B$, —$C(=S)R^A$, —$C(=S)N(R^B)_2$, —$NR^BC(=S)R^A$, —$S(O)R^A$, —SO_2R^A, —$NR^BSO_2R^A$, or —$SO_2N(R^B)_2$. In certain embodiments, R^2 is —$N(R^B)_2$. In certain embodiments, R^2 is —NHR^B. In certain embodiments, R^2 is —NH_2. In certain embodiments, R^2 is —OR^A. In certain embodiments, R^2 is —OH.

In certain embodiments, R^3 is hydrogen. In some embodiments, R^3 is not hydrogen. In some embodiments, R^3 is halo. In certain embodiments, R^3 is fluoro. In some embodiments, R^3 is optionally substituted aliphatic. In certain embodiments, R^3 is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^3 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^3 is substituted C_{1-6} alkyl. In certain embodiments, R^3 is $—CF_3$, CHF_2, or CH_2F. In certain embodiments, R^3 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^3 is methyl, ethyl, or propyl. In some embodiments, R^3 is —CN or $—NO_2$. In some embodiments, R^3 is optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl. In some embodiments, R^3 is —OR^A, —$N(R^B)_2$, —SR^A, —$C(=O)R^A$, —$C(O)OR^A$, —$C(O)SR^A$, —$C(O)N(R^B)_2$, —$OC(O)R^A$, —$NR^BC(O)R^A$, —$NR^BC(O)N(R^B)_2$, —$SC(O)R^A$, —$C(=NR^B)R^A$, —$C(=NR^B)N(R^B)_2$, —$NR^BC(=NR^B)R^B$, —$C(=S)R^A$, —$C(=S)N(R^B)_2$, —$NR^BC(=S)R^A$, —$S(O)R^A$, —SO_2R^A, —$NR^BSO_2R^A$, or —$SO_2N(R^B)_2$. In certain embodiments, R^3 is —$N(R^B)_2$. In certain embodiments, R^3 is —NHR^B. In certain embodiments, R^3 is —NH_2. In certain embodiments, R^3 is —OR^A. In certain embodiments, R^3 is —OH.

In some embodiments, R^2 and R^3 are the same. In some embodiments, R^2 and R^3 are different. In some embodiments, R^2 and R^3 are each hydrogen. In some embodiments, R^2 is hydrogen and R^3 is not hydrogen. In some embodiments, R^2 is hydrogen and R^3 is optionally substituted aliphatic. In some embodiments, R^2 is hydrogen and R^3 is C_{1-6} alkyl. In some embodiments, R^2 is hydrogen and R^3 is methyl. In some embodiments, R^2 is hydrogen and R^3 is ethyl or propyl. In some embodiments, R^2 is hydrogen and R^3 is $—CF_3$, CHF_2, or CH_2F. In some embodiments, R^2 is hydrogen and R^3 is —$N(R^B)_2$ or —OR^A. In some embodiments, R^2 is hydrogen and R^3 is $—NH_2$. In some embodiments, R^2 is hydrogen and R^3 is —OH. In some embodiments, R^2 and R^3 are not hydrogen. In some embodiments, R^2 and R^3 are independently optionally substituted aliphatic. In some embodiments, R^2 and R^3 are methyl. In some embodiments, R^2 and R^3 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring.

As defined generally above, R^4 and R^5 are independently selected from the group consisting of hydrogen, halo, —CN, $—NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)_2$, —SR^A, —$C(=O)R^A$, —$C(O)OR^A$, —$C(O)SR^A$, —$C(O)N(R^B)_2$, —$C(O)N(R^B)N(R^B)_2$, —$OC(O)R^A$, —$OC(O)N(R^B)_2$, —$NR^BC(O)R^A$, —$NR^BC(O)N(R^B)_2$, —$NR^BC(O)N(R^B)N(R^B)_2$, —$NR^BC(O)OR^A$, —$SC(O)R^A$, —$C(=NR^B)R^A$, —$C(=NNR^B)R^A$, —$C(=NOR^A)R^A$, —$C(=NR^B)N(R^B)_2$, —$NR^BC(=NR^B)R^B$, —$C(=S)R^A$, —$C(=S)N(R^B)_2$, —$NR^BC(=S)R^A$, —$S(O)R^A$, —$OS(O)_2R^A$, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$; or R^4 and R^5 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring. In certain embodiments, R^4 and R^5 are independently selected from the group consisting of hydrogen, halo, —CN, $—NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)^2$, —SR^A, —$C(=O)R^A$, —$C(O)OR^A$, —$C(O)SR^A$, —$C(O)N(R^B)_2$, —$OC(O)R^A$, —$NR^BC(O)R^A$, —$NR^BC(O)N(R^B)_2$, —$SC(O)R^A$, —$C(=NR^B)R^A$, —$C(=NR^B)N(R^B)_2$, —$NR^BC(=NR^B)R^B$, —$C(=S)R^A$, —$C(=S)N(R^B)_2$, —$NR^BC(=S)R^A$, —$S(O)R^A$, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$; or R^4 and R^5 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring.

In certain embodiments, R^4 is hydrogen. In some embodiments, R^4 is not hydrogen. In some embodiments, R^4 is halo. In certain embodiments, R^4 is fluoro. In some embodiments, R^4 is optionally substituted aliphatic. In certain embodiments, R^4 is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^4 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^4 is substituted C_{1-6} alkyl. In certain embodiments, R^4 is $—CF_3$, CHF_2, or CH_2F. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^4 is methyl, ethyl, or propyl. In some embodiments, R^4 is —CN or $—NO_2$. In some embodiments, R^4 is optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl. In some embodiments, R^4 is —OR^A, —$N(R^B)_2$, —SR^A, —$C(=O)R^A$, —$C(O)OR^A$, —$C(O)SR^A$, —$C(O)N(R^B)_2$, —$OC(O)R^A$, —$NR^BC(O)R^A$, —$NR^BC(O)N(R^B)_2$, —$SC(O)R^A$, —$C(=NR^B)R^A$, —$C(=NR^B)N(R^B)_2$, —$NR^BC(=NR^B)R^B$, —$C(=S)R^A$, —$C(=S)N(R^B)_2$, $NR^BC(=S)R^A$, $S(O)R^A$, —SO_2R^A, —$NR^BSO_2R^A$, or —$SO_2N(R^B)_2$. In certain embodiments, R^4 is —$N(R^B)_2$. In certain embodiments, R^4 is —NHR^B. In certain embodiments, R^4 is $—NH_2$. In certain embodiments, R^4 is —OR^A. In certain embodiments, R^4 is —OH.

In certain embodiments, R^5 is hydrogen. In some embodiments, R^5 is not hydrogen. In some embodiments, R^5 is halo. In certain embodiments, R^5 is fluoro. In some embodiments, R^5 is optionally substituted aliphatic. In certain embodiments, R^5 is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^5 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^5 is substituted C_{1-6} alkyl. In certain embodiments, R^5 is $—CF_3$, CHF_2, or CH_2F. In certain embodiments, R^5 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^5 is methyl, ethyl, or propyl. In some embodiments, R^5 is —CN or $—NO_2$. In some embodiments, R^5 is optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl. In some embodiments, R^5 is —OR^A, —$N(R^B)_2$, —SR^A, —$C(=O)R^A$, —$C(O)OR^A$, —$C(O)SR^A$, —$C(O)N(R^B)_2$, —$OC(O)R^A$, —$NR^BC(O)R^A$, —$NR^BC(O)N(R^B)_2$, —$SC(O)R^A$, —$C(=NR^B)R^A$, —$C(=NR^B)N(R^B)_2$, —$NR^BC(=NR^B)R^B$, —$C(=S)R^A$, —$C(=S)N(R^B)_2$, —$NR^BC(=S)R^A$, —$S(O)R^A$, —SO_2R^A, —$NR^BSO_2R^A$, or —$SO_2N(R^B)_2$. In certain embodiments, R^5 is —$N(R^B)_2$. In certain embodiments, R^5 is —NHR^B. In certain embodiments, R^5 is $—NH_2$. In certain embodiments, R^5 is —OR^A. In certain embodiments, R^5 is —OH.

In some embodiments, R^4 and R^5 are the same. In some embodiments, R^4 and R^5 are different. In some embodiments, R^4 and R^5 are each hydrogen. In some embodiments, R^4 is hydrogen and R^5 is not hydrogen. In some embodiments, R^4 is hydrogen and R^5 is optionally substituted aliphatic. In some embodiments, R^4 is hydrogen and R^5 is C_{1-6} alkyl. In some embodiments, R^4 is hydrogen and R^5 is methyl. In some embodiments, R^4 is hydrogen and R^5 is ethyl or propyl. In certain embodiments, R^4 and hydrogen and R^5 is $—CF_3$,

CHF_2, or CH_2F. In some embodiments, R^4 is hydrogen and R^5 is $—N(R^B)_2$ or $—OR^A$. In some embodiments, R^4 is hydrogen and R^5 is $—NH_2$. In some embodiments, R^4 is hydrogen and R^5 is —OH. In some embodiments, R^4 and R^5 are not hydrogen. In some embodiments, R^4 and R^5 are independently optionally substituted aliphatic. In some embodiments, R^4 and R^5 are methyl. In some embodiments, R^4 and R^5 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring.

As defined generally above, R^6 and R^7 are independently selected from the group consisting of hydrogen, halo, —CN, $—NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $—OR^A$, $—N(R^B)_2$, $—SR^A$, $—C(=O)R^A$, $—C(O)OR^A$, $—C(O)SR^A$, $—C(O)N(R^B)_2$, $—C(O)N(R^B)N(R^B)_2$, $—OC(O)R^A$, $—OC(O)N(R^B)_2$, $—NR^BC(O)R^A$, $—NR^BC(O)N(R^B)_2$, $—NR^BC(O)N(R^B)N(R^B)_2$, $—NR^BC(O)OR^A$, $—SC(O)R^A$, $—C(=NR^B)R^A$, $—C(=NNR^B)R^A$, $—C(=NOR^A)R^A$, $—C(=NR^B)N(R^B)_2$, $—NR^BC(=NR^B)R^B$, $—C(=S)R^A$, $—C(=S)N(R^B)_2$, $—NR^BC(=S)R^A$, $—S(O)R^A$, $—OS(O)_2R^A$, $—SO_2R^A$, $—NR^BSO_2R^A$, and $—SO_2N(R^B)_2$; or R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring. In certain embodiments, R^6 and R^7 are independently selected from the group consisting of hydrogen, halo, —CN, $—NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $—OR^A$, $—N(R^B)_2$, $—SR^A$, $—C(=O)R^A$, $—C(O)OR^A$, $—C(O)SR^A$, $—C(O)N(R^B)_2$, $—OC(O)R^A$, $—NR^BC(O)R^A$, $—NR^BC(O)N(R^B)_2$, $—SC(O)R^A$, $—C(=NR^B)R^A$, $—C(=NR^B)N(R^B)_2$, $—NR^BC(=NR^B)R^B$, $—C(=S)R^A$, $—C(=S)N(R^B)_2$, $—NR^BC(=S)R^A$, $—S(O)R^A$, $—SO_2R^A$, $—NR^BSO_2R^A$, and $—SO_2N(R^B)_2$; or R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring.

In certain embodiments, R^6 is hydrogen. In some embodiments, R^6 is not hydrogen. In some embodiments, R^6 is halo. In certain embodiments, R^6 is fluoro. In some embodiments, R^6 is optionally substituted aliphatic. In certain embodiments, R^6 is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^6 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^6 is substituted C_{1-6} alkyl. In certain embodiments, R^6 is $—CF_3$, CHF_2, or CH_2F. In certain embodiments, R^6 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^6 is methyl, ethyl, or propyl. In some embodiments, R^6 is —CN or $—NO_2$. In some embodiments, R^6 is optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl. In some embodiments, R^6 is $—OR^A$, $—N(R^B)_2$, $—SR^A$, $—C(=O)R^A$, $—C(O)OR^A$, $—C(O)SR^A$, $—C(O)N(R^B)_2$, $—OC(O)R^A$, $—NR^BC(O)R^A$, $—NR^BC(O)N(R^B)_2$, $—SC(O)R^A$, $—C(=NR^B)R^A$, $—C(=NR^B)N(R^B)_2$, $—NR^BC(=NR^B)R^B$, $—C(=S)R^A$, $—C(=S)N(R^B)_2$, $—NR^BC(=S)R^A$, $—S(O)R^A$, $—SO_2R^A$, $—NR^BSO_2R^A$, or $—SO_2N(R^B)_2$. In certain embodiments, R^6 is $—N(R^B)_2$. In certain embodiments, R^6 is $—NHR^B$. In certain embodiments, R^6 is $—NH_2$. In certain embodiments, R^6 is $—OR^A$. In certain embodiments, R^6 is —OH.

In certain embodiments, R^7 is hydrogen. In some embodiments, R^7 is not hydrogen. In some embodiments, R^7 is halo. In certain embodiments, R^7 is fluoro. In some embodiments, R^7 is optionally substituted aliphatic. In certain embodiments, R^7 is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^7 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^7 is substituted C_{1-6} alkyl. In certain embodiments, R^7 is $—CF_3$, CHF_2, or CH_2F. In certain embodiments, R^7 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^7 is methyl, ethyl, or propyl. In some embodiments, R^7 is —CN or $—NO_2$. In some embodiments, R^7 is optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl. In some embodiments, R^7 is $—OR^A$, $—N(R^B)_2$, $—SR^A$, $—C(=O)R^A$, $—C(O)OR^A$, $—C(O)SR^A$, $—C(O)N(R^B)_2$, $—OC(O)R^A$, $—NR^BC(O)R^A$, $—NR^BC(O)N(R^B)_2$, $—SC(O)R^A$, $—C(=NR^B)R^A$, $—C(=NR^B)N(R^B)_2$, $—NR^BC(=NR^B)R^B$, $—C(=S)R^A$, $—C(=S)N(R^B)_2$, $—NR^BC(=S)R^A$, $—S(O)R^A$, $—SO_2R^A$, $—NR^BSO_2R^A$, or $—SO_2N(R^B)_2$. In certain embodiments, R^7 is $—N(R^B)_2$. In certain embodiments, R^7 is $—NHR^B$. In certain embodiments, R^7 is $—NH_2$. In certain embodiments, R^7 is $—OR^A$. In certain embodiments, R^7 is —OH.

In some embodiments, R^6 and R^7 are the same. In some embodiments, R^6 and R^7 are different. In some embodiments, R^6 and R^7 are each hydrogen. In some embodiments, R^6 is hydrogen and R^7 is not hydrogen. In some embodiments, R^6 is hydrogen and R^7 is optionally substituted aliphatic. In some embodiments, R^6 is hydrogen and R^7 is C_{1-6} alkyl. In some embodiments, R^6 is hydrogen and R^7 is methyl. In some embodiments, R^6 is hydrogen and R^7 is ethyl or propyl. In certain embodiments, R^6 and hydrogen and R^7 is $—CF_3$, CHF_2, or CH_2F. In some embodiments, R^6 is hydrogen and R^7 is $—N(R^B)_2$ or $—OR^A$. In some embodiments, R^6 is hydrogen and R^7 is $—NH_2$. In some embodiments, R^6 is hydrogen and R^7 is —OH. In some embodiments, R^6 and R^7 are not hydrogen. In some embodiments, R^6 and R^7 are independently optionally substituted aliphatic. In some embodiments, R^6 and R^7 are methyl. In some embodiments, R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring.

As defined generally above, R^8, R^9, R^{10}, and R^{11} are independently hydrogen, halo, or optionally substituted aliphatic. In some embodiments, R^8, R^9, R^{10}, and R^{11} are hydrogen. In some embodiments, R^9, R^{10}, and R^{11} are hydrogen, and R^8 is optionally substituted aliphatic. In some embodiments, R^9, R^{10}, and R^{11} are hydrogen, and R^8 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^9, R^{10}, and R^{11} are hydrogen, and R^8 is optionally substituted C_{1-3} aliphatic. In some embodiments, R^9, R^{10}, and R^{11} are hydrogen, and R^8 is methyl. In some embodiments, R^8, R^9, and R^{10} are hydrogen, and R^{11} is optionally substituted aliphatic. In some embodiments, R^8, R^9, and R^{10} are hydrogen, and R^{11} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^8, R^9, and R^{10} are hydrogen, and R^{11} is optionally substituted C_{1-3} aliphatic. In some embodiments, R^8, R^9, and R^{10} are hydrogen, and R^{11} is methyl. In some embodiments, R^8 is hydrogen. In some embodiments, R^8 is halo. In certain embodiments, R^8 is fluoro. In some embodiments, R^8 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^8 is optionally substituted C_{1-3} alkyl. In certain embodiments, R^8 is methyl. In some embodiments, R^9 is hydrogen. In some embodiments, R^9 is halo. In certain embodiments, R^9 is fluoro. In some embodiments, R^9 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^9 is optionally substituted C_{1-3} alkyl. In certain embodiments, R^9 is methyl. In some embodiments, R^{10} is hydrogen. In some embodiments, R^{10} is halo. In certain embodiments, R^{10} is fluoro. In some embodiments, R^{10} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{10} is optionally substituted C_{1-3} alkyl. In certain embodiments, R^{10} is methyl. In some embodiments, R^{11} is hydrogen. In some embodiments, R^{11} is halo. In certain embodiments, R^{11} is fluoro. In some embodiments, R^{11} is optionally substi-

tuted C_{1-6} aliphatic. In some embodiments, R^{11} is optionally substituted C_{1-3} alkyl. In certain embodiments, R^{11} is methyl.

As defined generally above, Cy is a monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy is unsubstituted. In certain embodiments, Cy is substituted with one or two R^y groups. In certain embodiments, Cy is substituted with one R^y group. In certain embodiments, Cy is substituted with two R^y groups. In certain embodiments, Cy is substituted with three R^y groups. In certain embodiments, Cy is substituted with four R^y groups.

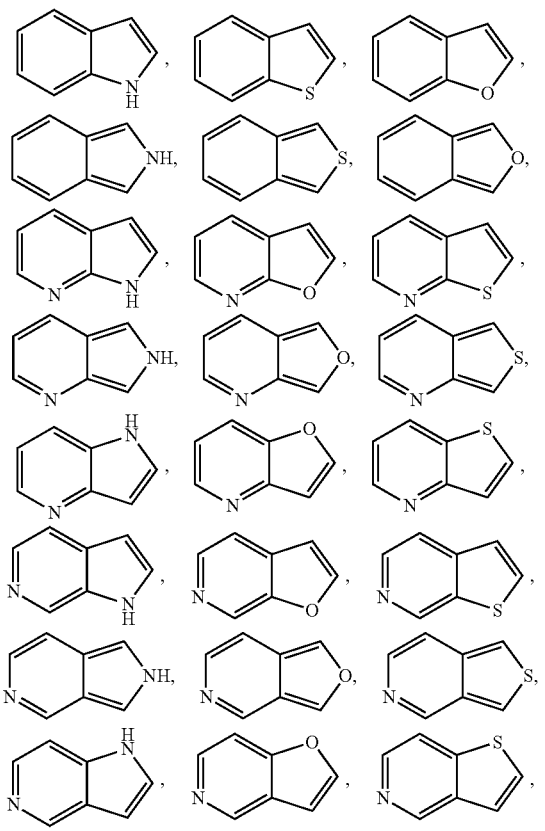
In certain embodiments, Cy is phenyl substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy is phenyl substituted with one or two R^y groups. In certain embodiments, Cy is unsubstituted phenyl. In certain embodiments, Cy is phenyl substituted with one R^y group. In certain embodiments, Cy is phenyl substituted with two R^y groups. In certain embodiments, Cy is phenyl substituted with three R^y groups. In certain embodiments, Cy is phenyl substituted with four R^y groups.

In certain embodiments, Cy is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy is an unsubstituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Cy is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and is substituted with one or two R^y groups. In certain embodiments, Cy is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and is substituted with one R^y group. In certain embodiments, Cy is a 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyrazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl), and is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy is a 6-membered heteroaryl having 1-3 nitrogens (e.g., pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl), and is substituted with 0, 1, 2, 3, or 4 R^y groups.

In certain embodiments, Cy is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy is an 8- to 12-membered bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy is an unsubstituted bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Cy is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with one or two R^y groups. In certain embodiments, Cy is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with one R^y group. In certain embodiments, Cy is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with two R^y groups. In certain embodiments, Cy is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with three R^y groups. In certain embodiments, Cy is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with four R^y groups.

In certain embodiments, Cy is an 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy is a 9-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl), wherein Cy is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy is a 10-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., naphthyridinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl), wherein Cy is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy is selected from the group consisting of quinoline, benzimidazole, benzopyrazole, quinoxaline, tetrahydroquinoline, tetrahydroisoquinoline, naphthalene, tetrahydronaphthalene, 2,3-dihydrobenzo[b][1,4]dioxine, isoindole, 2H-benzo[b][1,4]oxazin-3(4H)-one, 3,4-dihydro-2H-benzo[b][1,4]oxazine, and quinoxalin-2(1H)-one, wherein Cy is substituted with 0, 1, 2, 3, or 4 R^y groups.

In certain embodiments, Cy is a 5,6-fused bicyclic heteroaryl ring system such as one of the following:



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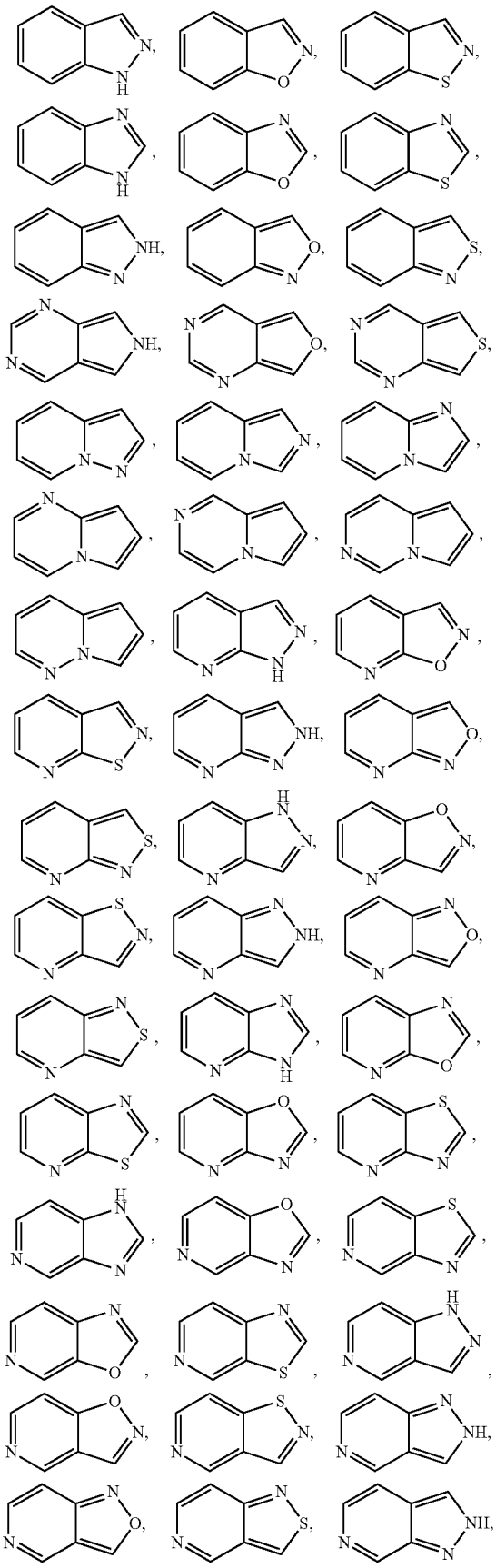

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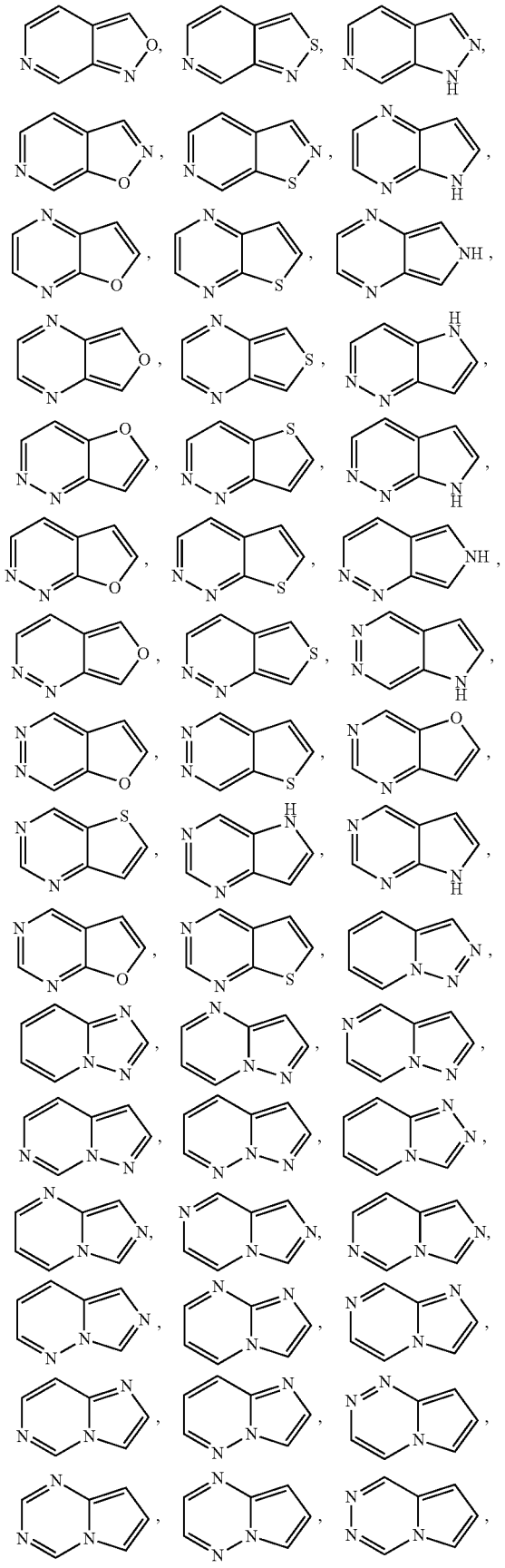

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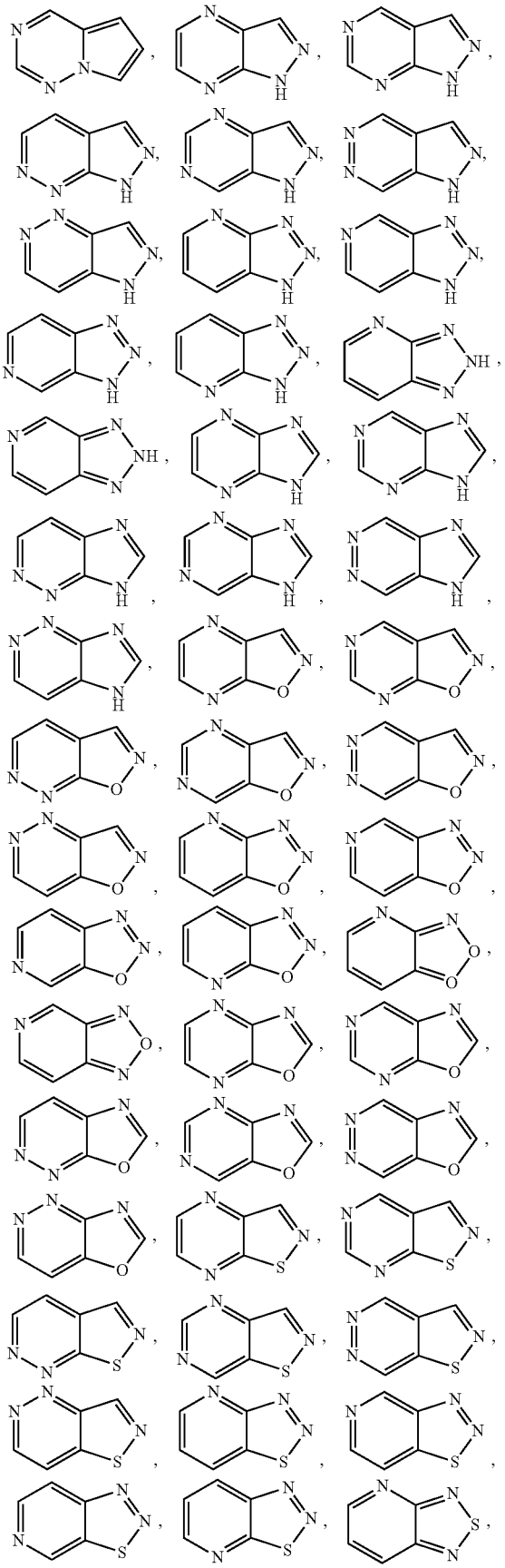

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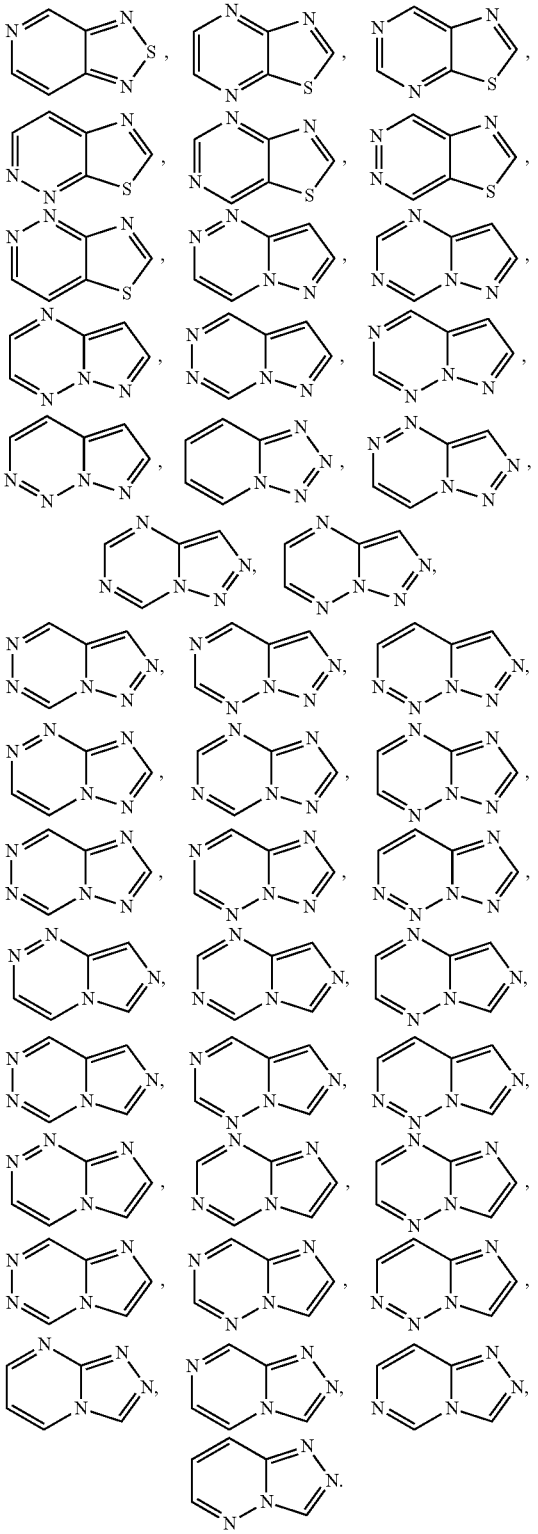
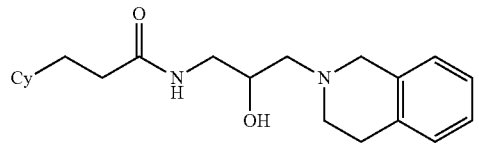


In any bicyclic heteroaryl group shown above, the point of attachment can be any carbon or nitrogen atom, as valency permits, and the ring may be substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits.

In certain embodiments, a provided compound is of Formula (VII):

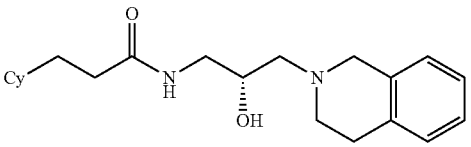
VII



or a pharmaceutically acceptable salt thereof, wherein Cy is a 5,6-fused bicyclic heteroaryl as described herein, wherein Cy is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits.

In certain embodiments, a provided compound is of Formula (VII-a):

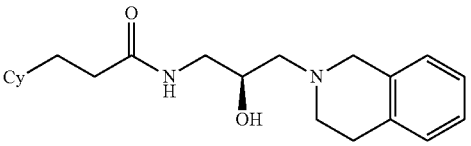
VII-a



or a pharmaceutically acceptable salt thereof, wherein Cy is a 5,6-fused bicyclic heteroaryl as described herein, wherein Cy is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits.

In certain embodiments, a provided compound is of Formula (VII-b):

VII-b



or a pharmaceutically acceptable salt thereof, wherein Cy is a 5,6-fused bicyclic heteroaryl as described herein, wherein Cy is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits.

As defined generally above, each R^y is independently selected from the group consisting of halo, —CN, —NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)_2$, —SR^A, —$C(=O)R^A$, —$C(O)OR^A$, —$C(O)SR^A$, —$C(O)N(R^B)_2$, —$C(O)N(R^B)N(R^B)_2$, —$OC(O)R^A$, —$OC(O)N(R^B)_2$, —$NR^BC(O)R^A$, —$NR^BC(O)N(R^B)_2$, —$NR^BC(O)N(R^B)N(R^B)_2$, —$NR^BC(O)OR^A$, —$SC(O)R^A$, —$C(=NR^B)R^A$, —$C(=NNR^B)R^A$, —$C(=NOR^A)R^A$, —$C(=NR^B)N(R^B)_2$, —$NR^BC(=NR^B)R^B$, —$C(=S)R^A$, —$C(=S)N(R^B)_2$, —$NR^BC(=S)R^A$, —$S(O)R^A$, —$OS(O)_2R^A$, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$, wherein R^A and R^B are described herein; or an R^y group may be optionally taken together with R^2 or R^3 to form an optionally substituted 5- to 6-membered carbocyclic or heterocyclic ring fused to Cy. In some embodiments, each R^y is independently selected from the group consisting of halo, —CN, —NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)_2$, —SR^A, —$C(=O)R^A$, —$C(O)OR^A$, —$C(O)SR^A$, —$C(O)N(R^B)_2$, —$OC(O)R^A$, —$NR^BC(O)R^A$, —$NR^BC(O)N(R^B)_2$, —$SC(O)R^A$, —$C(=NR^B)R^A$, —$C(=NR^B)N(R^B)_2$, —$NR^BC(=NR^B)R^B$, —$C(=S)R^A$, —$C(=S)N(R^B)_2$, —$NR^BC(=S)R^A$, —$S(O)R^A$, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$, wherein R^A and R^B are described herein.

In some embodiments, at least one R^y is halo. In certain embodiments, at least one R^y is fluoro. In certain embodiments, at least one R^y is chloro. In some embodiments, at least one R^y is —CN. In some embodiments, at least one R^y is —OR^A, wherein R^A is optionally substituted aliphatic. In some embodiments, at least one R^y is —OR^A, wherein R^A is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one R^y is methoxy, ethoxy, or propoxy. In certain embodiments, at least one R^y is methoxy. In some embodiments, at least one R^y is —OR^A, wherein R^A is substituted C_{1-6} alkyl. In certain embodiments, at least one R^y is —$OCH_2CH_2N(CH_3)_2$. In some embodiments, at least one R^y is —$N(R^B)_2$. In some embodiments, at least one R^y is —$N(R^B)_2$, wherein each R^B is independently selected from hydrogen or C_{1-6} alkyl. In some embodiments, at least one R^y is —NHR^B. In some embodiments, at least one R^y is —$N(C_{1-6}$ alkyl$)_2$, —$NH(C_{1-6}$ alkyl), or —NH_2. In certain embodiments, at least one R^y is —NH_2. In certain embodiments, at least one R^y is —$NHCH_3$. In certain embodiments, at least one R^y is —$N(CH_3)_2$.

In some embodiments, at least one R^y is optionally substituted aliphatic. In certain embodiments, at least one R^y is substituted aliphatic. In certain embodiments, at least one R^y is unsubstituted aliphatic. In some embodiments, at least one R^y is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one R^y is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one R^y is substituted C_{1-6} alkyl. In certain embodiments, at least one R^y is methyl, ethyl, or propyl. In certain embodiments, at least one R^y is methyl. In certain embodiments, at least one R^y is —CF_3, CHF_2, or CH_2F. In certain embodiments, at least one R^y is C_{1-6} alkyl substituted with aryl, heteroaryl, or heterocyclyl. In certain embodiments, at least one R^y is benzyl. In certain embodiments, at least one R^y is —(C_{1-6} alkyl)-heteroaryl. In certain embodiments, at least one R^y is —(C_{1-6} alkyl)-heterocyclyl. In certain embodiments, at least one R^y is —CH_2-heteroaryl. In certain embodiments, at least one R^y is —CH_2-heterocyclyl.

In some embodiments, at least one R^y is —$C(O)N(R^B)_2$. In certain embodiments, at least one R^y is —$C(O)NHR^B$. In certain embodiments, at least one R^y is —$C(O)NH_2$. In certain embodiments, at least one R^y is —$C(O)N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted 5- to 6-membered heterocyclyl. In certain embodiments, at least one R^y is —$C(O)N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted morpholinyl.

In some embodiments, at least one R^y is —$SO_2N(R^B)_2$. In certain embodiments, at least one R^y is —SO_2NHR^B. In certain embodiments, at least one R^y is —SO_2NH_2. In certain embodiments, at least one R^y is —$SO_2N(R^B)_2$, wherein neither R^B is hydrogen. In certain embodiments, at least one R^y is —$SO_2NH(C_{1-6}$ alkyl) or —$SO_2N(C_{1-6}$ alkyl$)_2$. In certain embodiments, at least one R^y is —$SO_2N(CH_3)_2$. In certain embodiments, at least one R^y is —$SO_2N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted 5- to 6-membered heterocyclyl. In certain embodiments, at least one R^y is —SO_2-morpholinyl. In certain embodiments, at least one R^y is —SO_2-piperidinyl, —SO_2-piperazinyl, or —SO_2-piperidinyl.

In some embodiments, at least one R^y is —SO_2R^A. In some embodiments, at least one R^y is —SO_2R^A, wherein R^A is optionally substituted aliphatic. In some embodiments, at

least one R^y is $—SO_2(C_{1-6}$ alkyl). In some embodiments, at least one R^y is $—SO_2CH_3$. In some embodiments, at least one R^y is $—C(O)R^A$. In some embodiments, at least one R^y is $—C(O)R^A$, wherein R^A is optionally substituted aliphatic. In some embodiments, at least one R^y is $—C(O)(C_{1-6}$ alkyl). In some embodiments, at least one R^y is $—C(O)CH_3$.

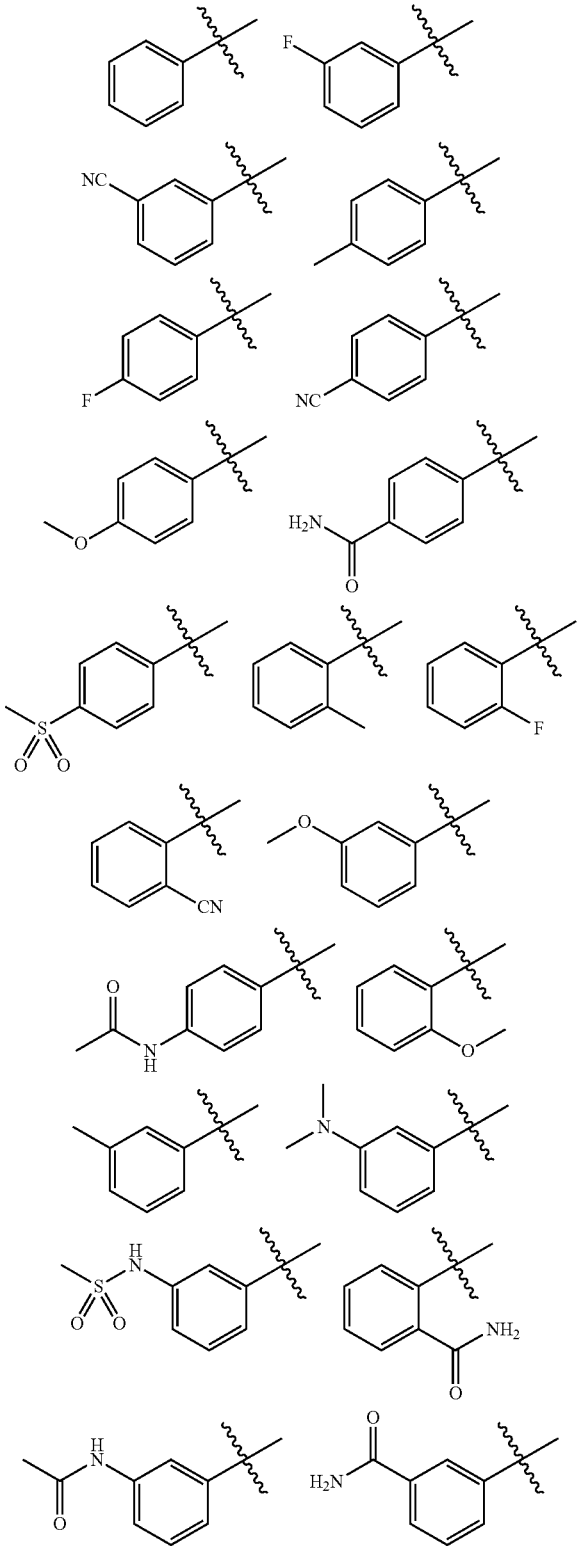
In some embodiments, at least one R^y is $—N(R^B)C(O)R^A$. In certain embodiments, at least one R^y is $—NHC(O)R^A$. In certain embodiments, at least one R^y is $—NHC(O)(C_{1-6}$ alkyl). In certain embodiments, at least one R^y is $—NHC(O)CH_3$.

In some embodiments, at least one R^y is $—N(R^B)SO_2R^A$. In some embodiments, at least one R^y is $—NHSO_2R^A$. In some embodiments, at least one R^y is $—(C_{1-6}$ alkyl)SO_2R^A. In certain embodiments, at least one R^y is $—NHSO_2(C_{1-6}$ alkyl) or $—N(C_{1-6}$ alkyl)$SO_2(C_{1-6}$ alkyl). In certain embodiments, at least one R^y is $—NHSO_2CH_3$. In certain embodiments, at least one R^y is $—N(CH_3)SO_2CH_3$.

In some embodiments, at least one R^y is optionally substituted heterocyclyl, optionally substituted carbocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, at least one R^y is an optionally substituted 5- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted pyrrolidinyl. In certain embodiments, at least one R^y is pyrroldinyl, hydroxypyrrolidinyl, or methylpyrrolidinyl. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted piperidinyl. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted piperdinyl, optionally substituted piperazinyl, or optionally substituted morpholinyl. In certain embodiments, at least one R^y is morpholinyl, tetrahydropyranyl, piperidinyl, methylpiperidinyl, piperazinyl, methylpiperazinyl, acetylpiperazinyl, methylsulfonylpiperazinyl, aziridinyl, or methylaziridinyl. In some embodiments, at least one R^y is an optionally substituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 6-membered heteroaryl having 1-3 nitrogens. In certain embodiments, at least one R^y is an optionally substituted pyrazolyl. In certain embodiments, at least one R^y is an optionally substituted imidazolyl. In certain embodiments, at least one R^y is an optionally substituted pyridyl. In certain embodiments, at least one R^y is an optionally substituted pyrimidyl. In certain embodiments, at least one R^y is pyrazolyl, methylpyrazolyl, imidazolyl, or methylimidazolyl.

In some embodiments, an R^y group is taken together with R^2 or R^3 and their intervening atoms to form a 5- to 6-membered carbocyclic or heterocyclic ring fused to Cy.

In certain embodiments, Cy is selected from the group consisting of:



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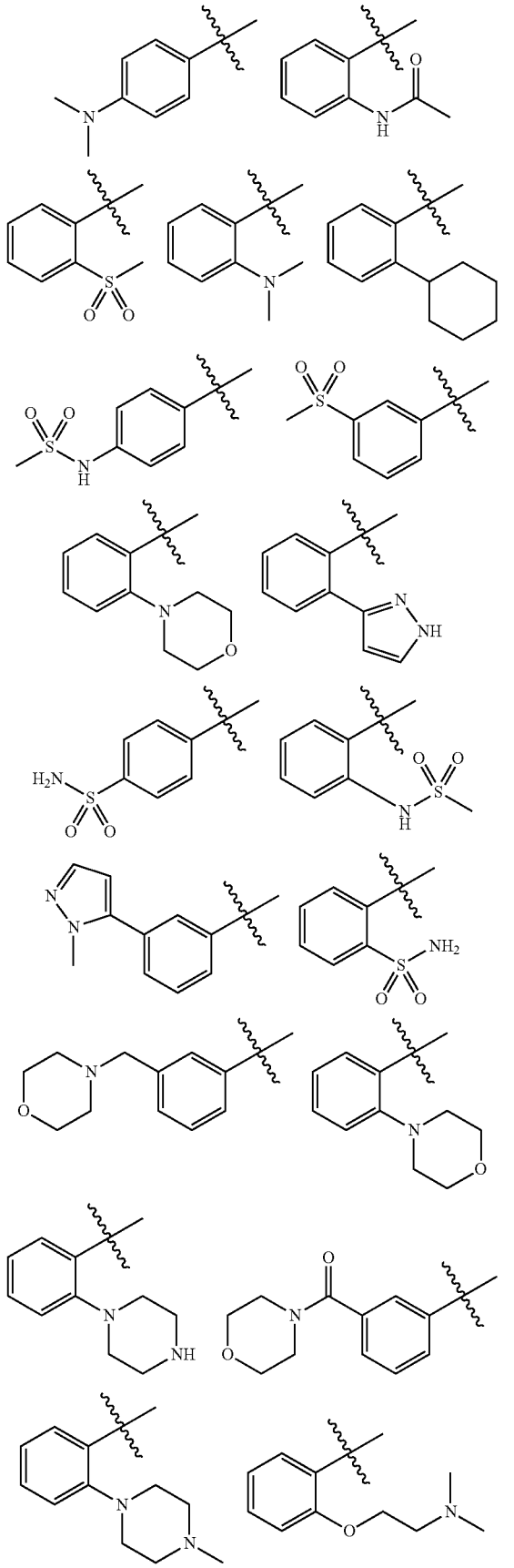

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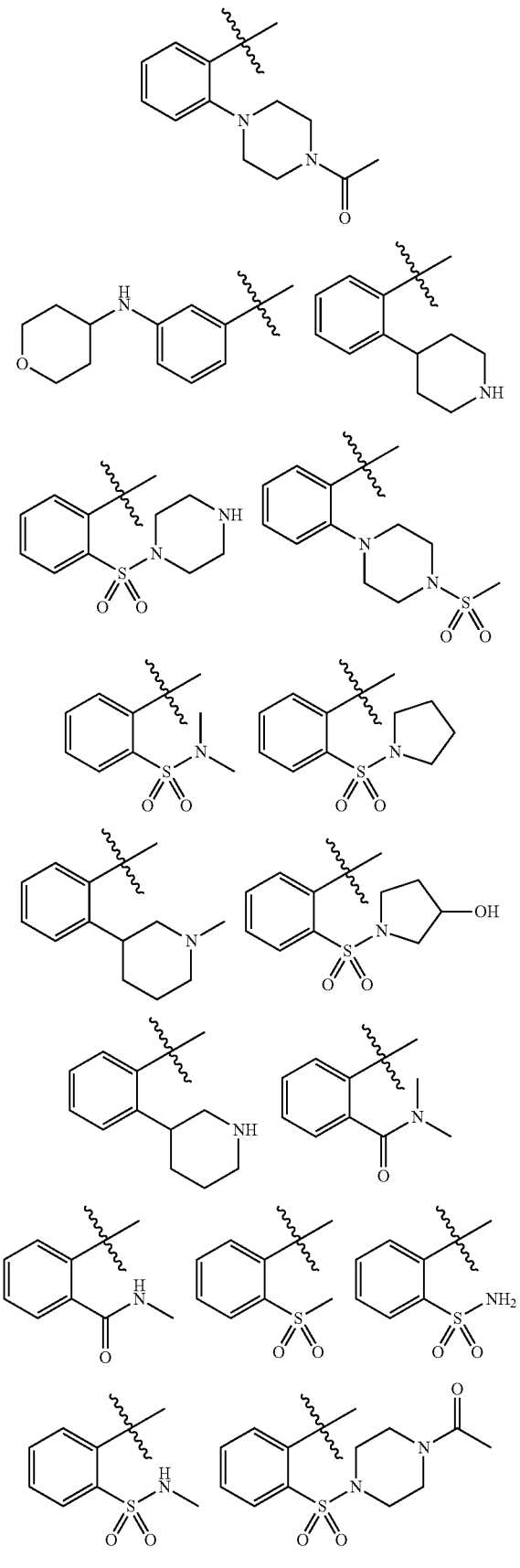

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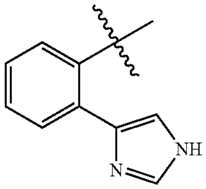
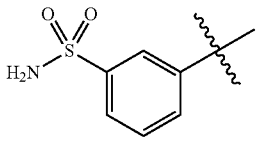
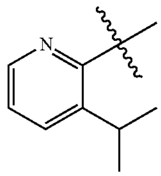
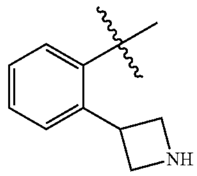
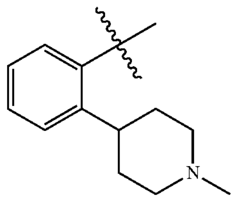
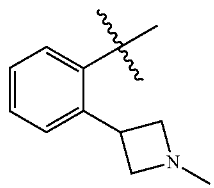
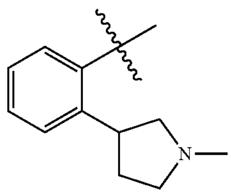
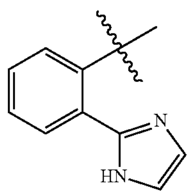
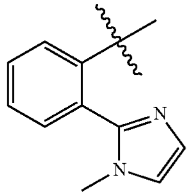
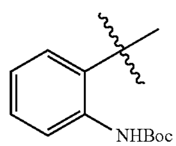
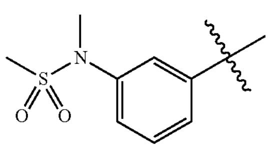
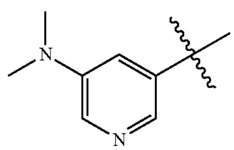
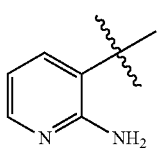
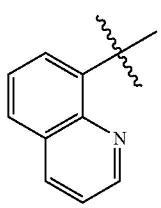
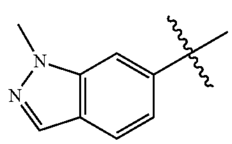
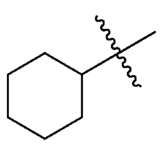
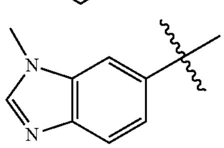
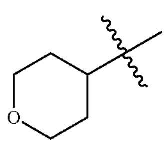
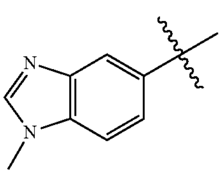
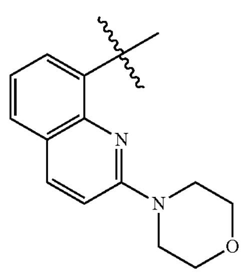

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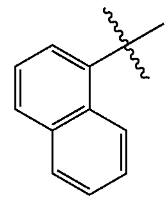
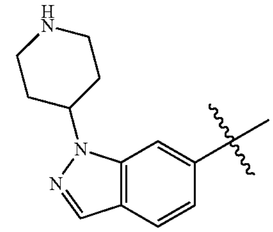
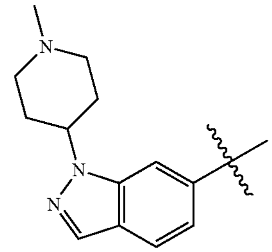
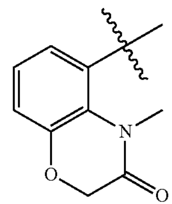
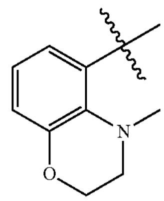
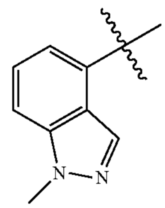
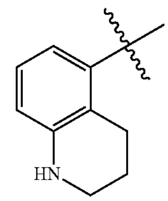
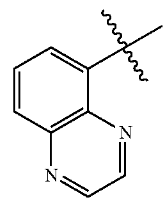
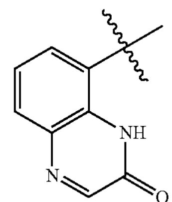
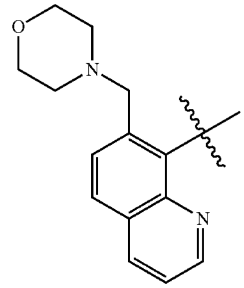
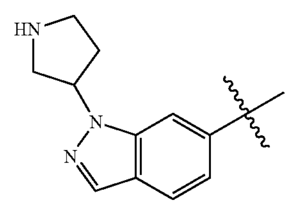
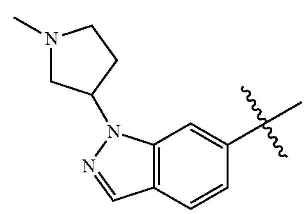
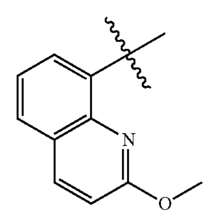
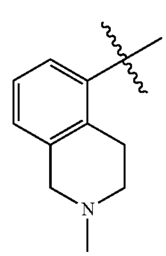
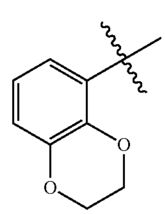
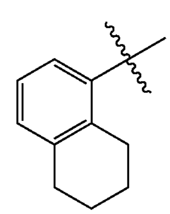

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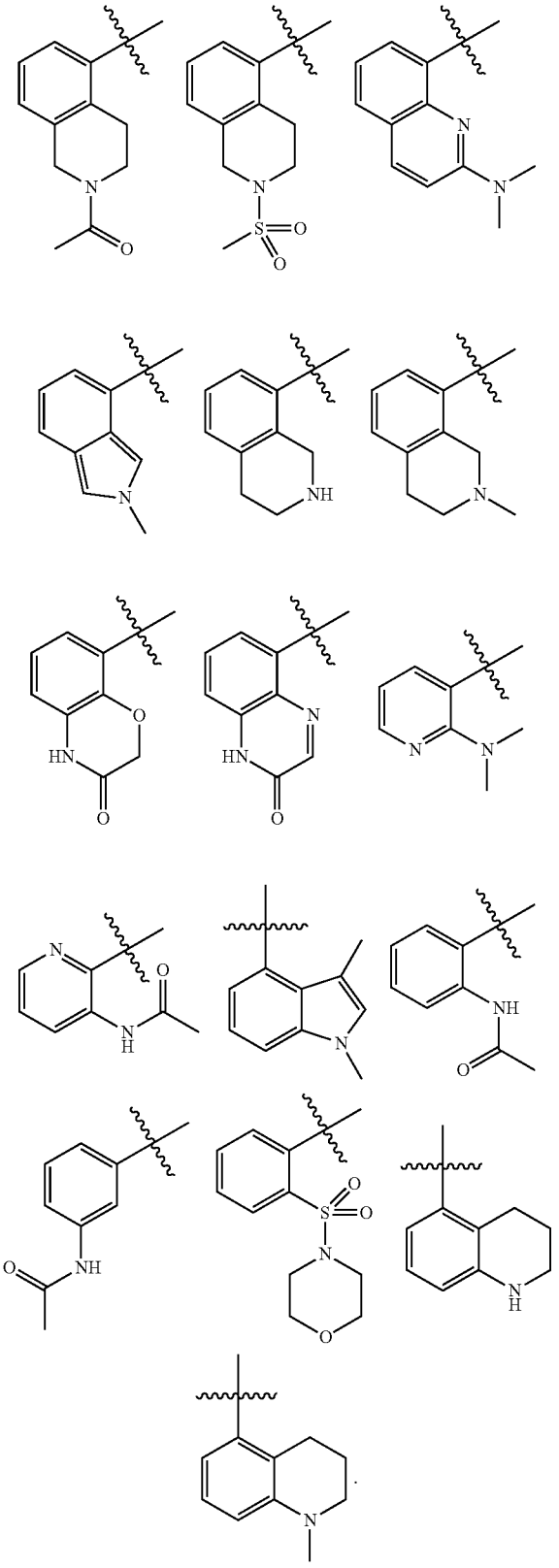

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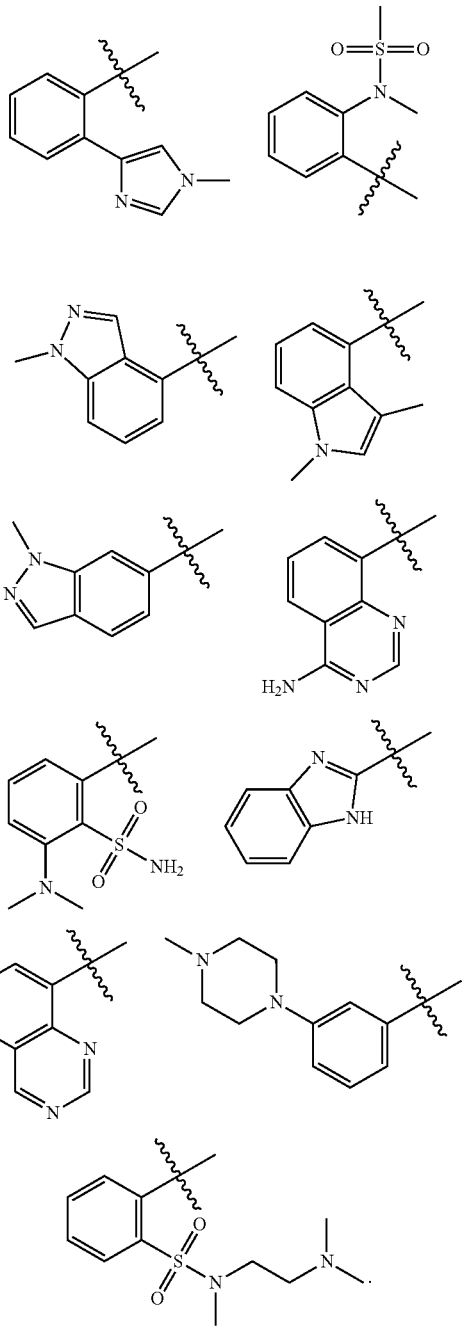
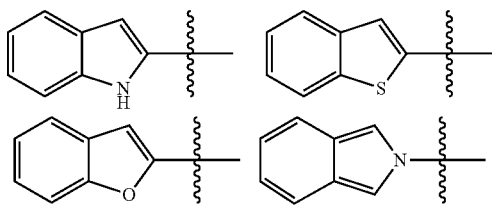


In some embodiments, Cy is selected from the group consisting of:



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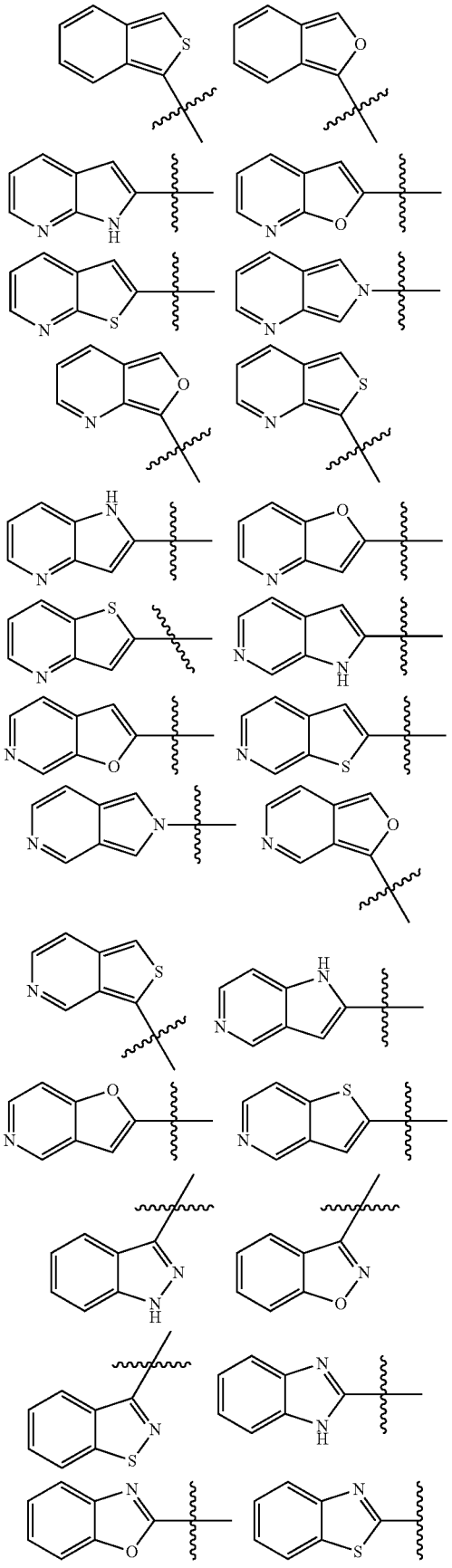

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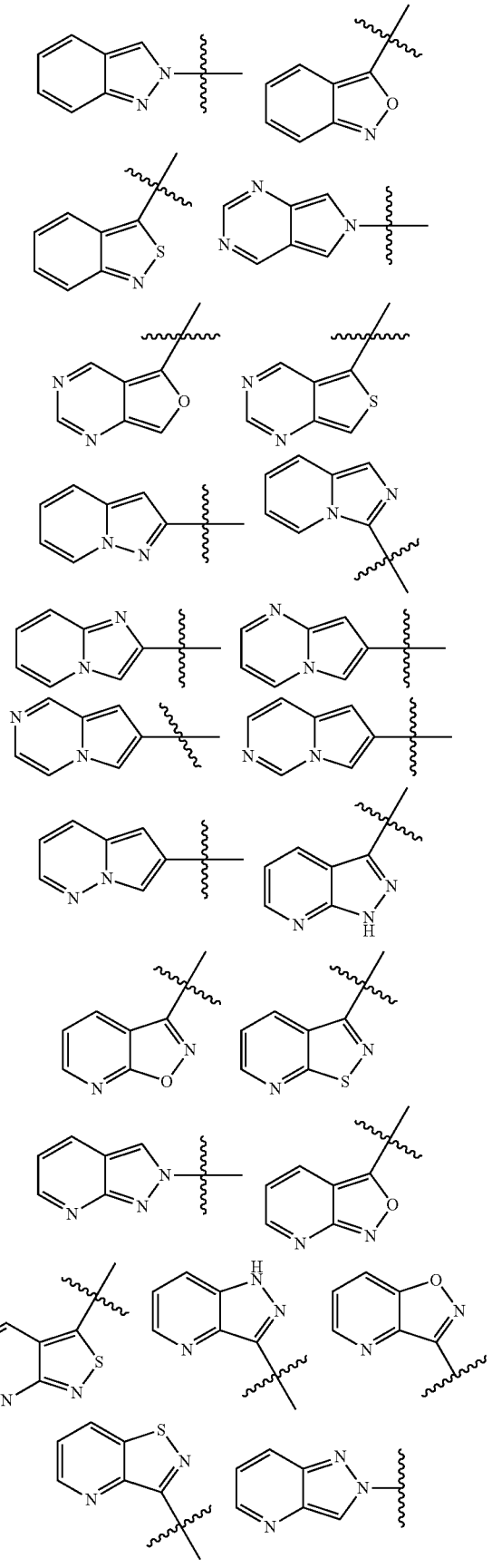

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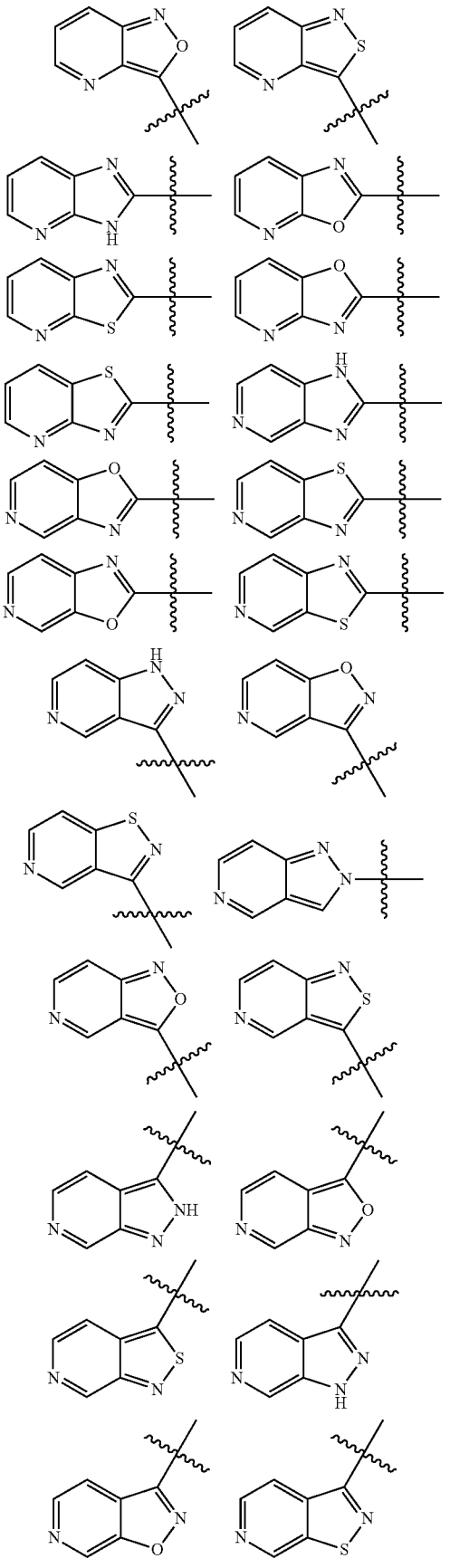

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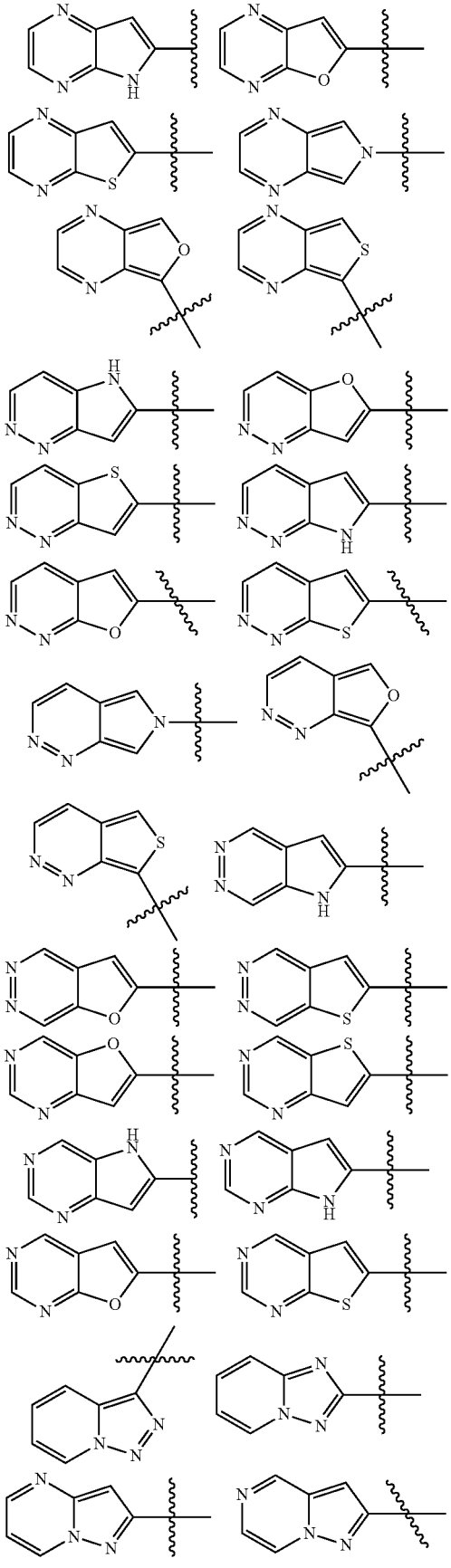
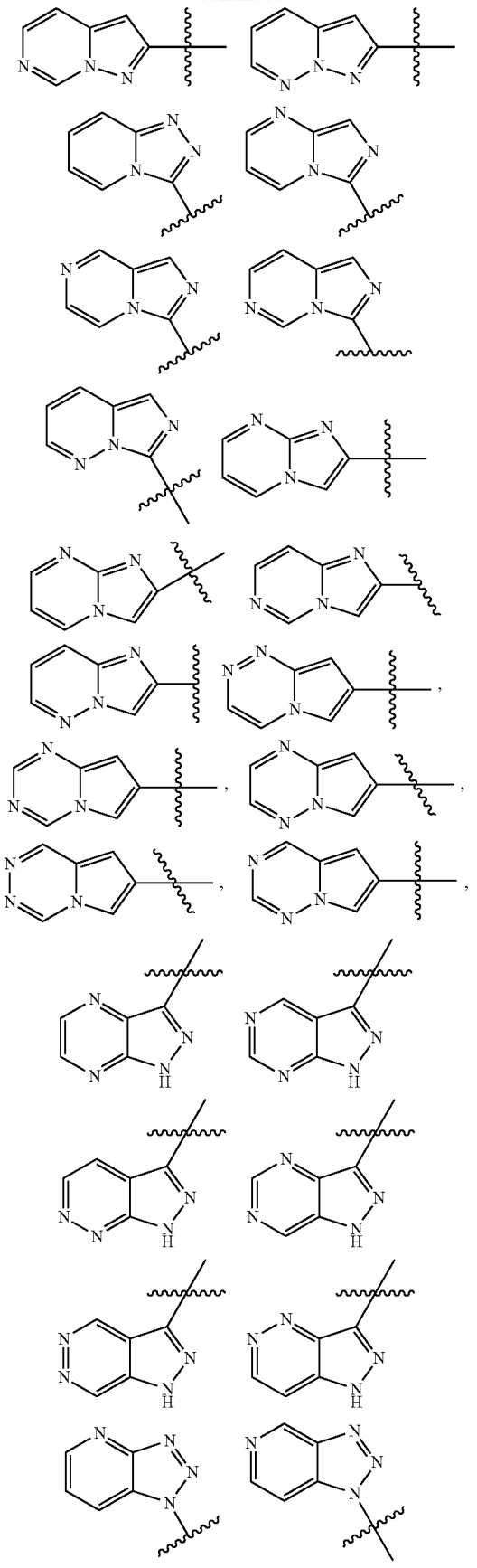


-continued



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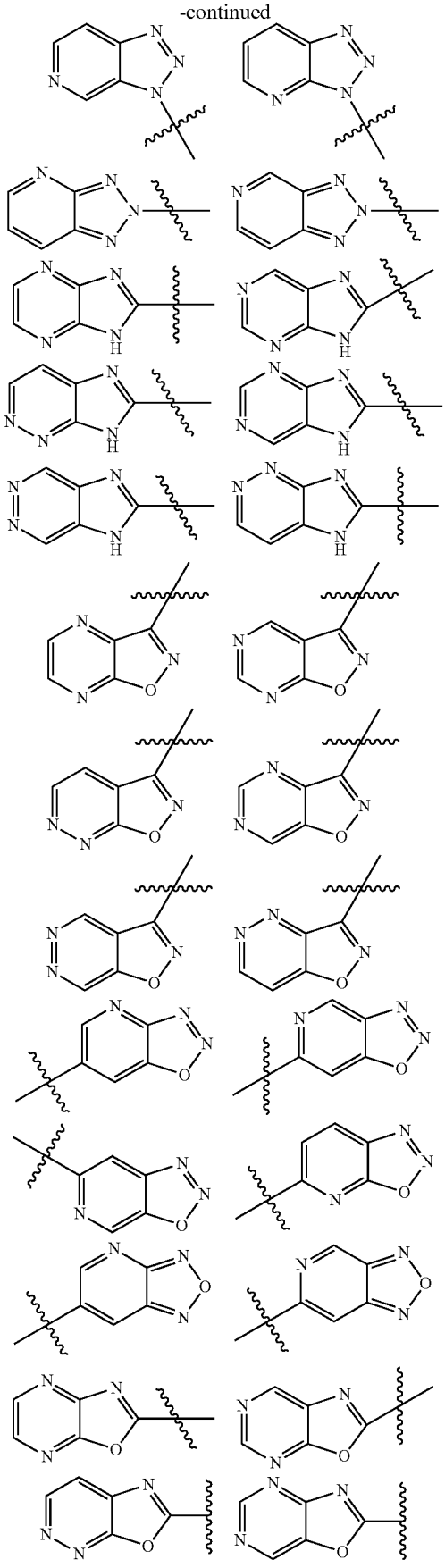

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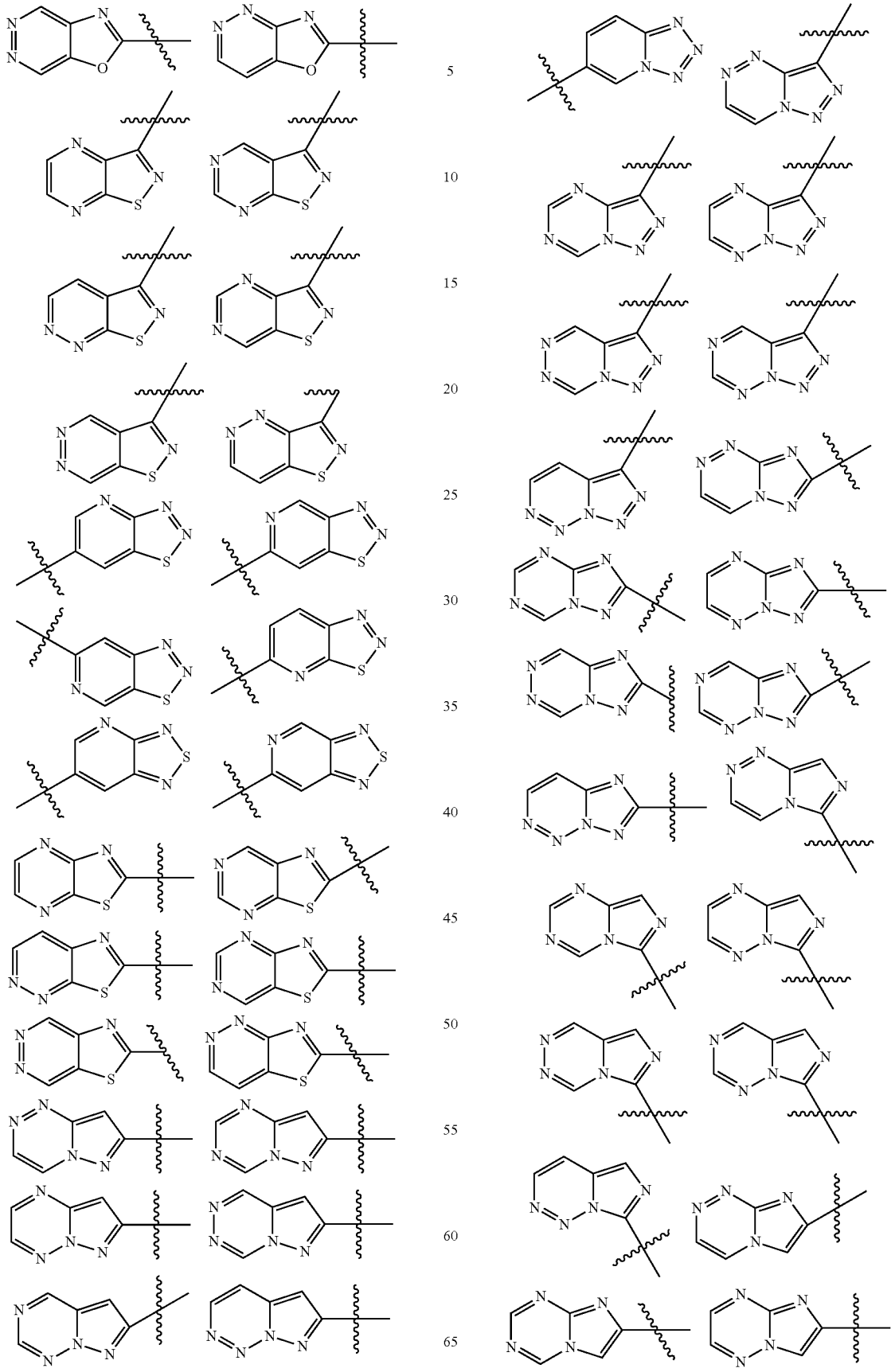
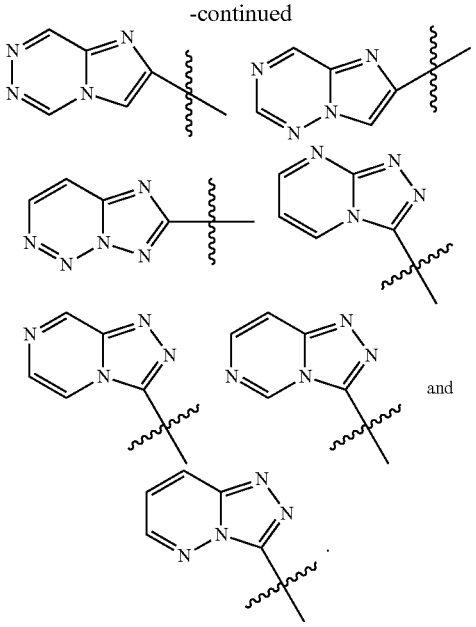


-continued

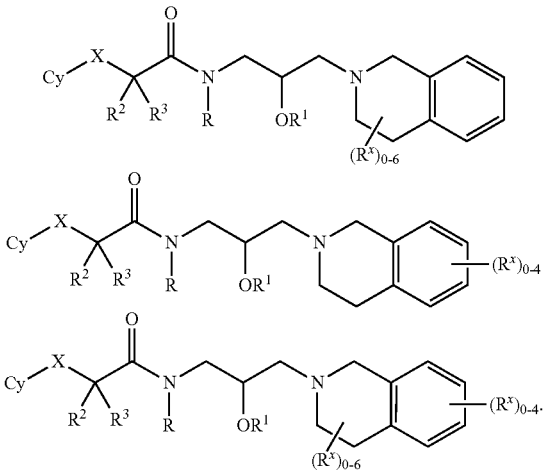
-continued



and

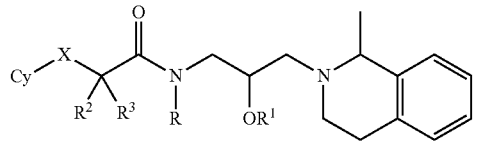
As defined generally above, each R^x is independently selected from the group consisting of halo, —CN, optionally substituted aliphatic, —OR', and —$N(R")_2$. In certain embodiments, at least one R^x is halo. In certain embodiments, at least one R^x is fluoro. In certain embodiments, at least one R^x is —CN. In certain embodiments, at least one R^x is optionally substituted aliphatic. In certain embodiments, at least one R^x is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one R^x is methyl. In certain embodiments, at least one R^x is —CF_3. In certain embodiments, at least one R^x is —OR' or —$N(R")_2$. In certain embodiments, R^x is not —OR' or —$N(R")_2$. In certain embodiments, at least one R^x is —OCH_3. In certain embodiments, R^x is not —OCH_3.

One of ordinary skill in the art will appreciate that an R^x group can be attached anywhere on the tetrahydroisoquinoline or dihydroisoquinoline ring. In certain embodiments, an R^x group is attached to the benzene portion of the tetrahydroisoquinoline or dihydroisoquinoline ring. In certain embodiments, an R^x group is attached to the tetrahydropyridine or dihydropyridine portion of the tetrahydroisoquinoline or dihydroisoquinoline ring. In certain embodiments, R^x groups are attached to both the benzene portion and the tetrahydropyridine (or dihydropyridine) portion of the tetrahydroisoquinoline (or dihydroisoquinoline) ring. See, for example, the structures shown below:



In certain embodiments, a provided compound is of Formula (VI):

VI



or a pharmaceutically acceptable salt thereof.

As defined generally above, n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2.

In certain embodiments, a provided compound is a compound listed in Table 1, or a pharmaceutically acceptable salt thereof.

TABLE 1

Exemplary Compounds

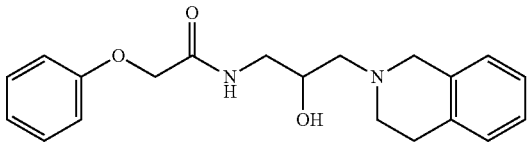
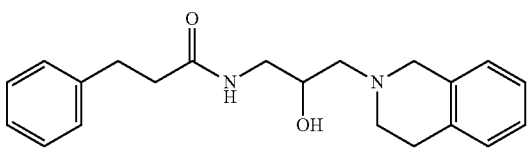
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
1		340.1787	341.2
2		338.1994	339.2

TABLE 1-continued

Exemplary Compounds

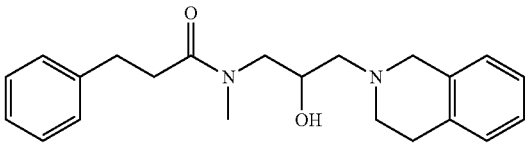
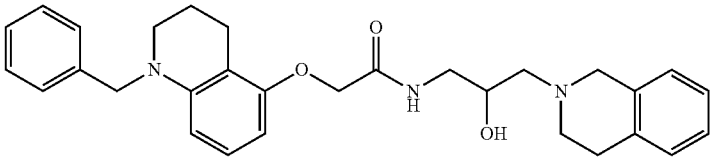
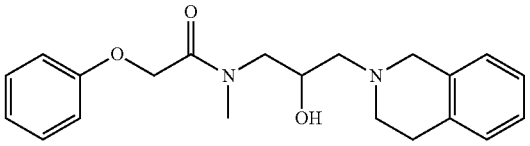
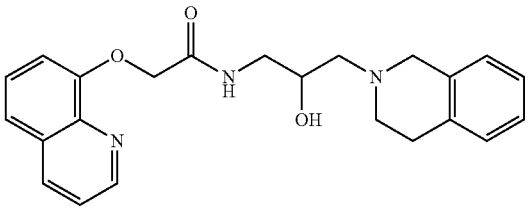
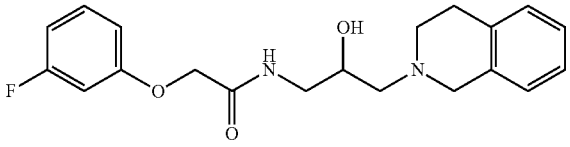
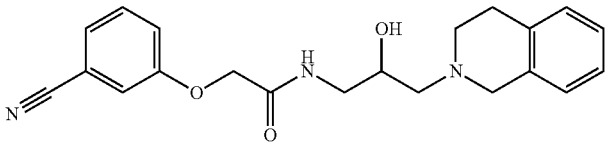
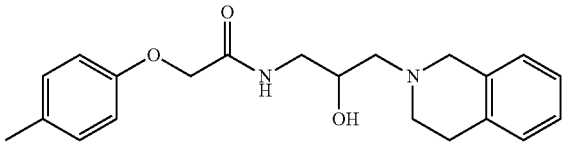
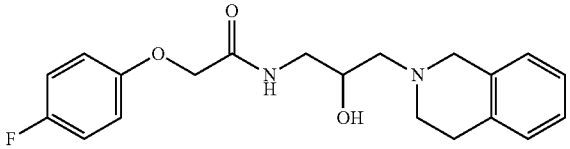
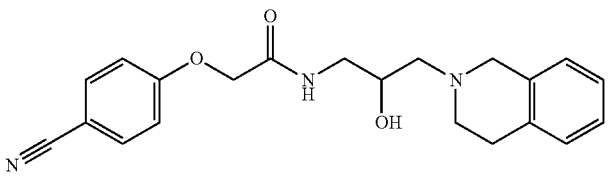
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
3		352.2151	353.2
4		485.2678	486.2
5		354.1943	355.1
6		391.1896	392.2
7		358.1693	359.1
8		365.1739	366.1
9		354.1943	355.2
10		358.1693	359.2
11		365.1739	366.2

TABLE 1-continued

Exemplary Compounds

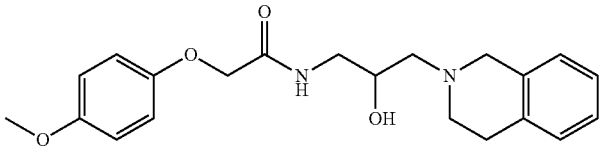
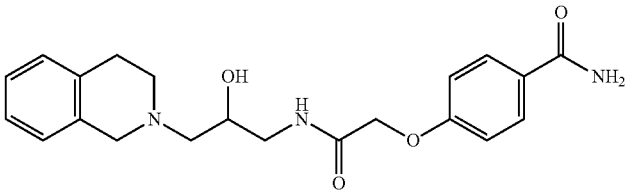
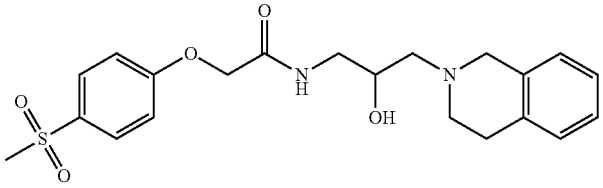
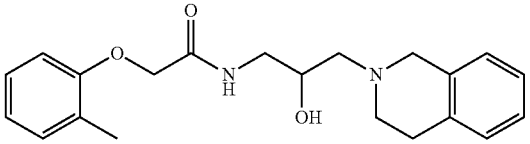
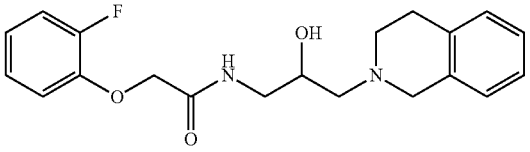
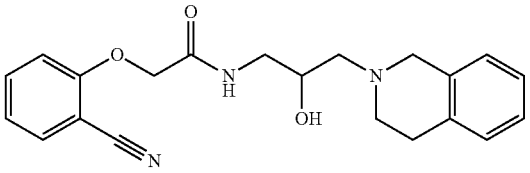
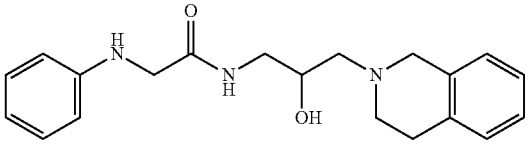
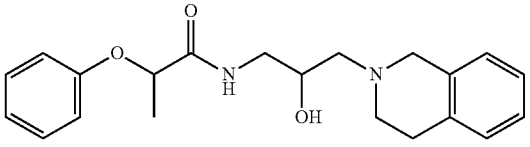
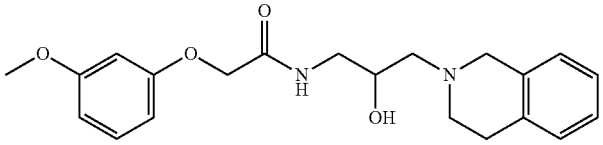
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
12		370.1893	371.2
13		383.1845	384.2
14		418.1562	419.2
15		354.1943	355.1
16		358.1693	359.1
17		365.1739	366.1
18		339.1947	340.1
19		354.1943	355.2
20		370.1893	371.1

TABLE 1-continued

Exemplary Compounds

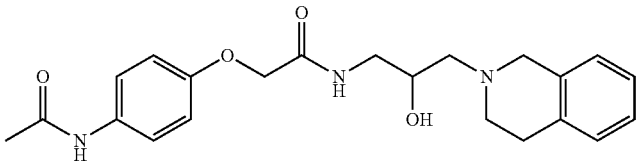
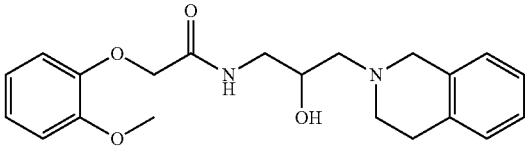
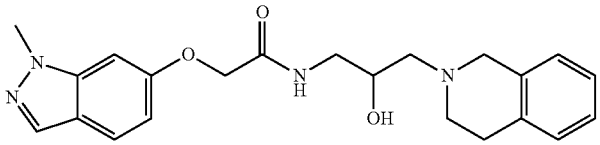
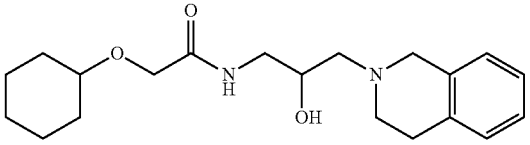
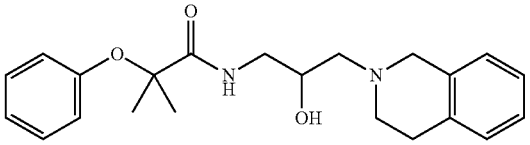
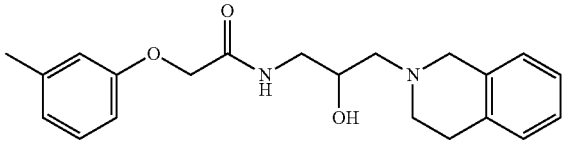
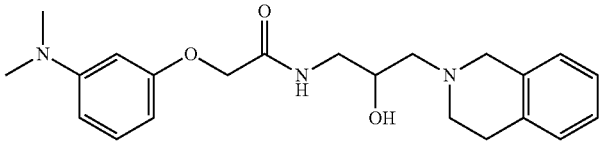
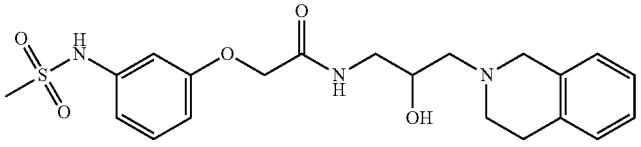
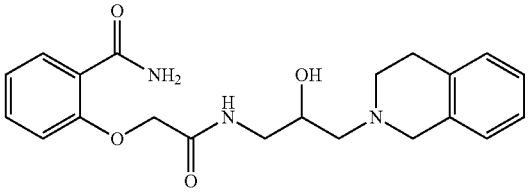
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
21		397.2002	398.2
22		370.1893	371.1
23		394.2005	395.1
24		346.2256	347.2
25		368.21	369.2
26		354.1943	355.2
27		383.2209	384.2
28		433.1671	434.1
29		383.1845	384.2

TABLE 1-continued

Exemplary Compounds

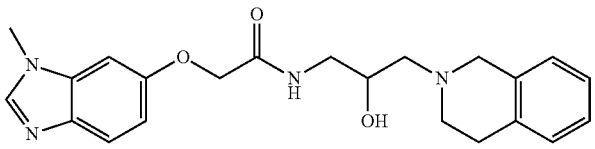
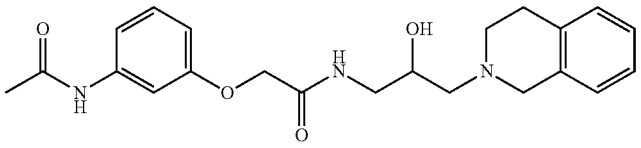
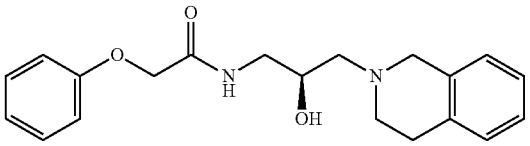
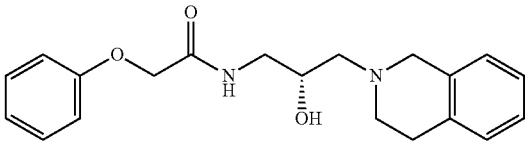
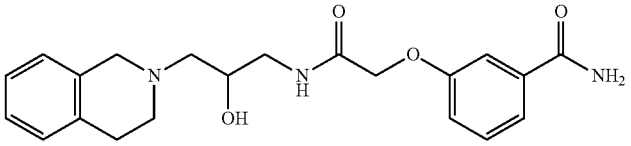
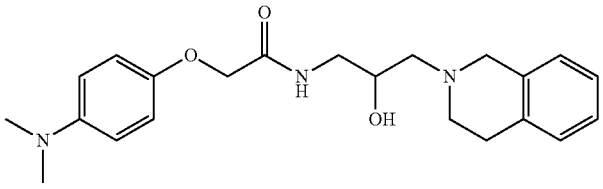
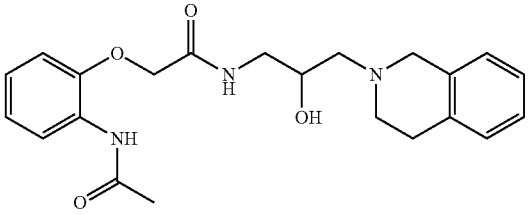
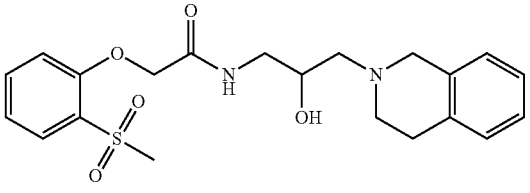
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
30		394.2005	395.1
31		397.2002	398.1
32		340.1787	341.2
33		340.1787	341.2
34		383.1845	384.1
35		383.2209	384.2
36		397.2002	398.1
37		418.1562	419.1

TABLE 1-continued

Exemplary Compounds

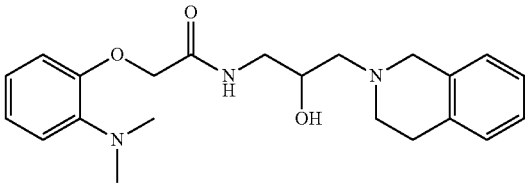
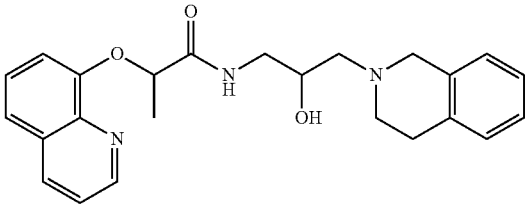
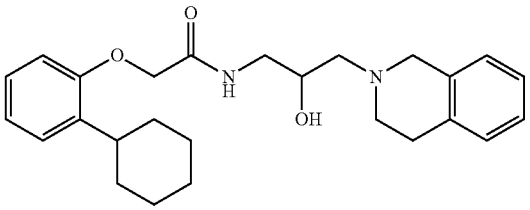
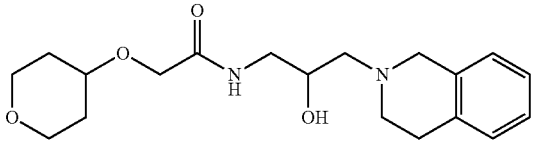
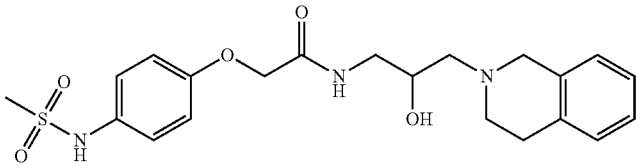
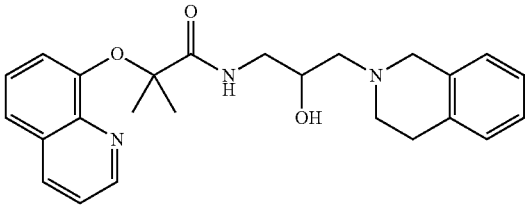
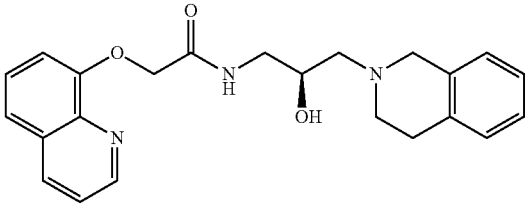
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
38		383.2209	384.2
39		405.2052	406.2
40		422.2569	423.2
41		348.2049	349.2
42		433.1671	434.1
43		419.2209	420.2
44		391.1896	392.1

TABLE 1-continued

Exemplary Compounds

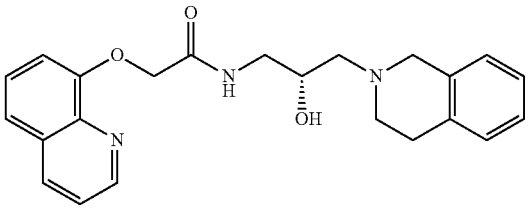
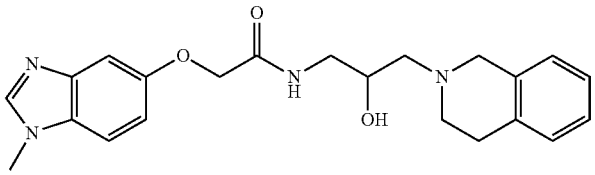
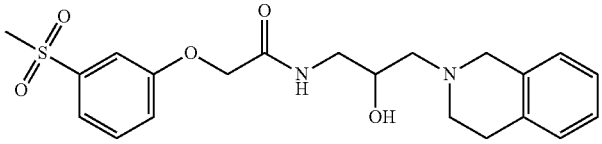
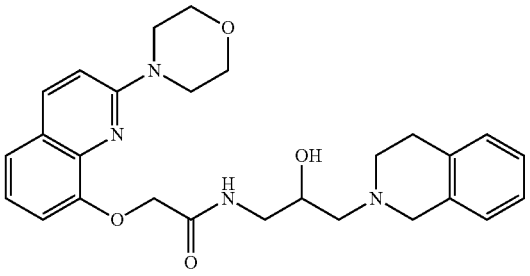
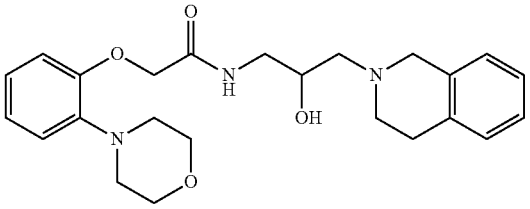
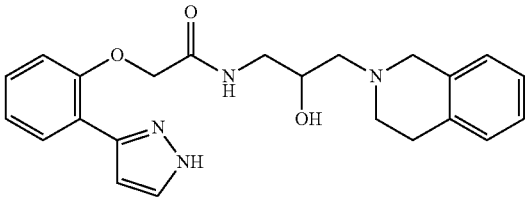
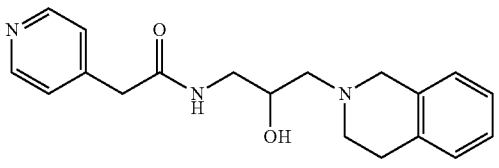
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
45		391.1896	392.1
46		394.2005	395.2
47		418.1562	419.1
48		476.2424	477.2
49		425.2315	426.2
50		406.2005	407.2
51		325.179	326.1

TABLE 1-continued

Exemplary Compounds

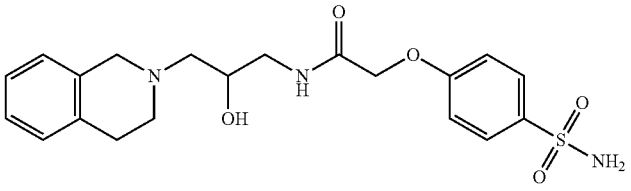
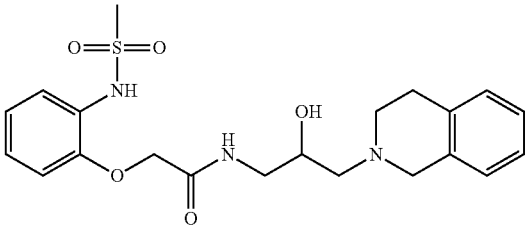
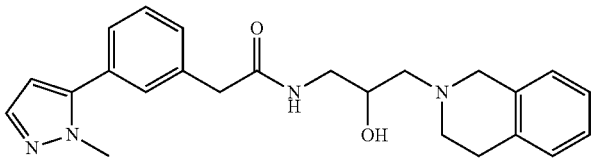
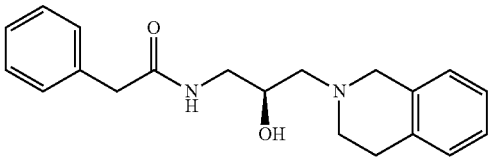
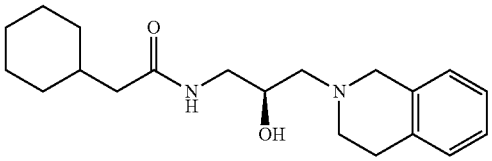
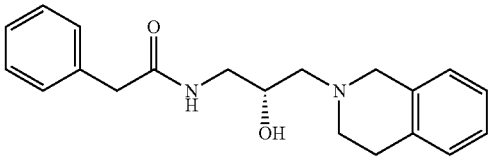
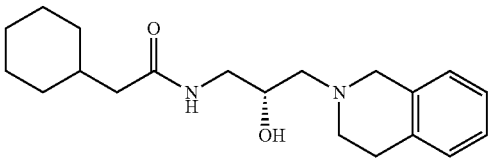
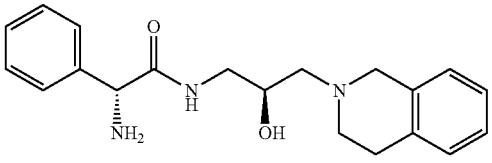
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
52		419.1515	420.1
53		433.1671	434.1
54		404.2212	405.2
55		324.1838	325.1
56		330.2307	331.2
57		324.1838	325.1
58		330.2307	331.2
59		339.1947	340.2

TABLE 1-continued

Exemplary Compounds

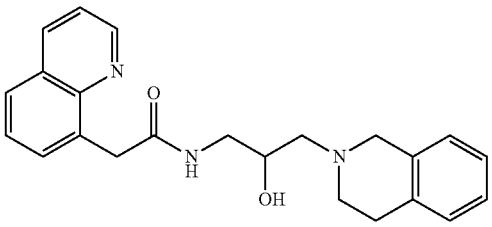
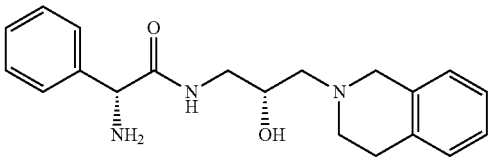
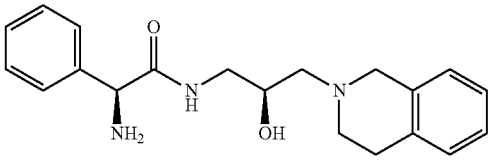
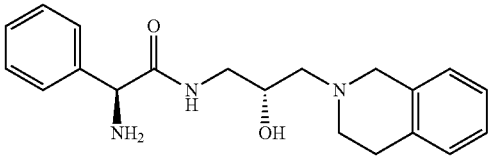
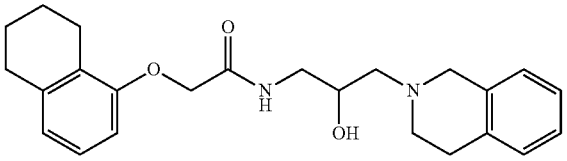
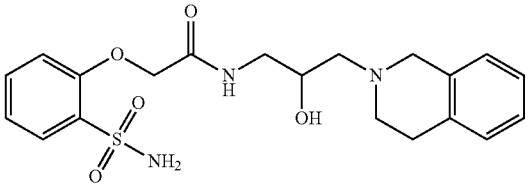
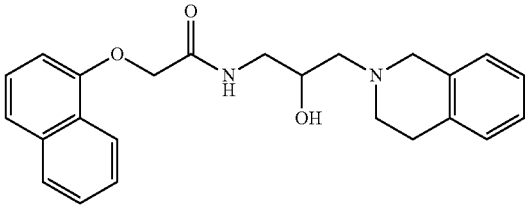
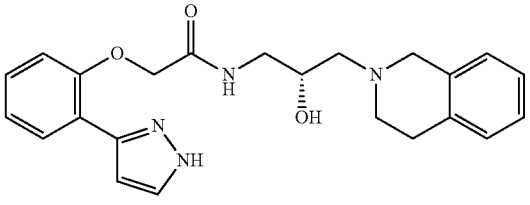
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
60		375.1947	376.1
61		339.1947	340.1
62		339.1947	340.1
63		339.1947	340.1
64		394.2256	395.1
65		419.1515	420.1
66		390.1943	391.2
67		406.2005	407.2

TABLE 1-continued

Exemplary Compounds

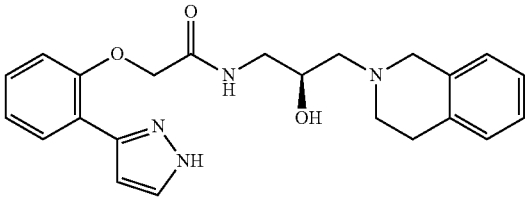
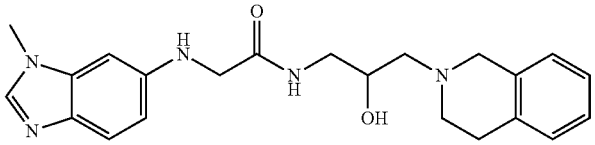
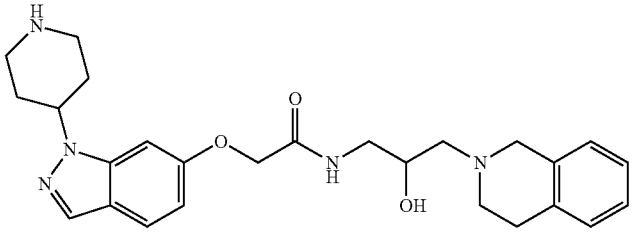
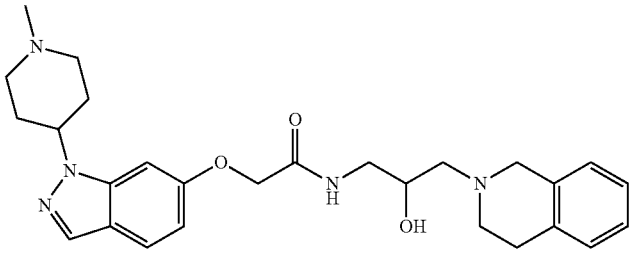
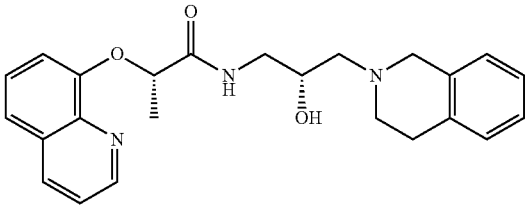
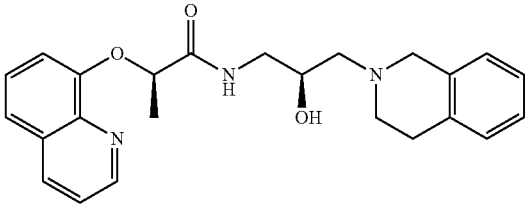
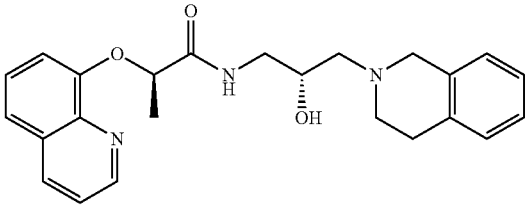
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
68		406.2005	407.2
69		393.2165	394.2
70		463.2583	464.2
71		477.274	478.3
72		405.2052	406.2
73		405.2052	406.1
74		405.2052	406.1

TABLE 1-continued

Exemplary Compounds

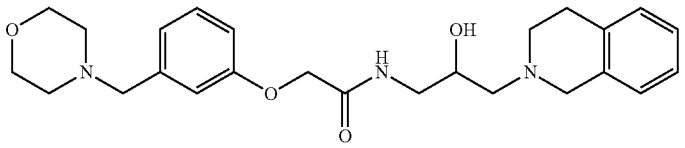
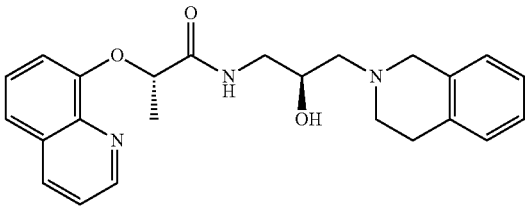
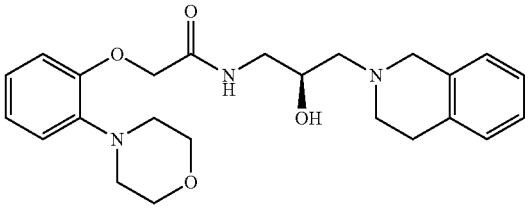
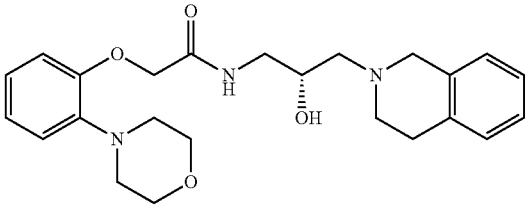
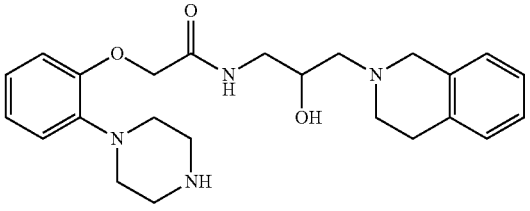
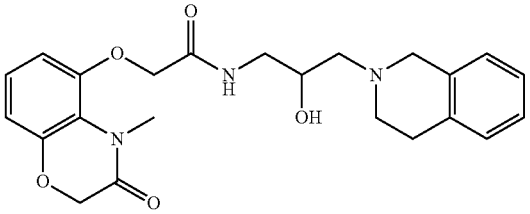
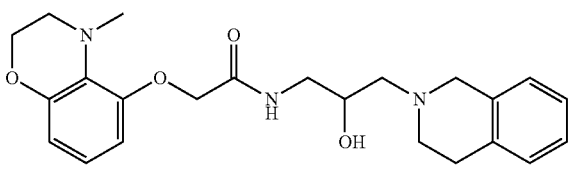
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
75		439.2471	440.2
76		405.2052	406.2
77		425.2315	426.2
78		425.2315	426.2
79		424.2474	425.2
80		425.1951	426.2
81		411.2158	412.1

TABLE 1-continued

Exemplary Compounds

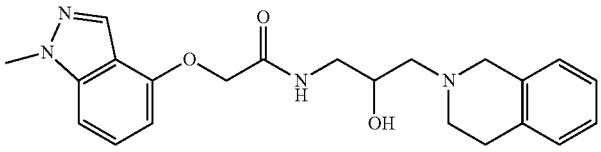
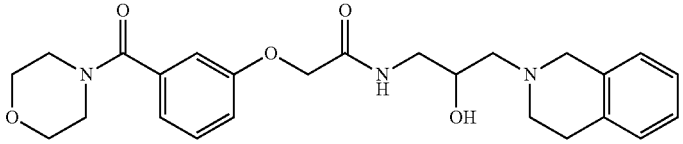
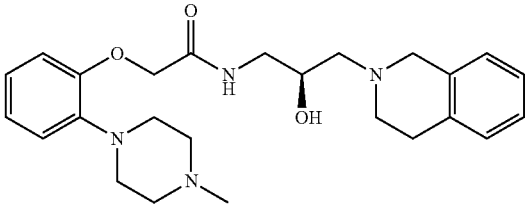
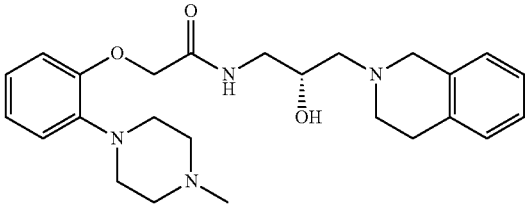
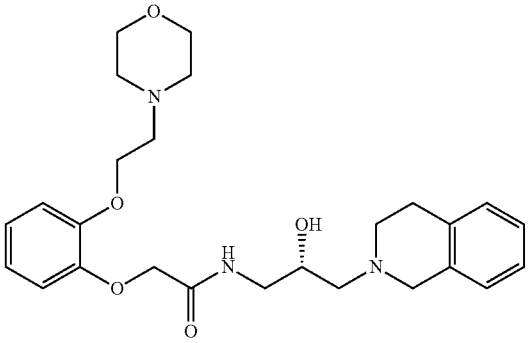
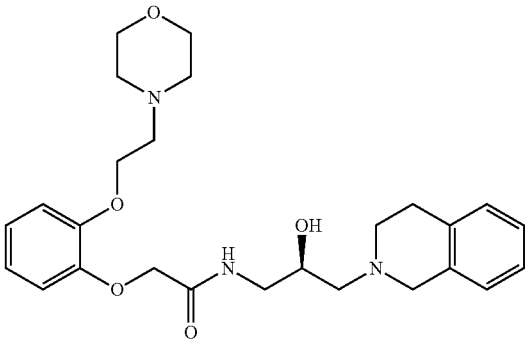
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
82		394.2005	395.2
83		453.2264	454.2
84		438.2631	439.3
85		438.2631	439.3
86		469.2577	470.2
87		469.2577	470.2

TABLE 1-continued

Exemplary Compounds

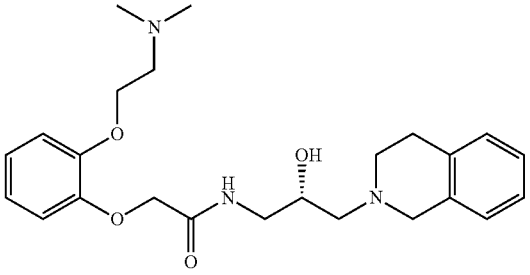
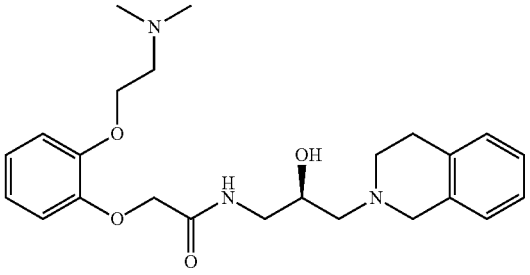
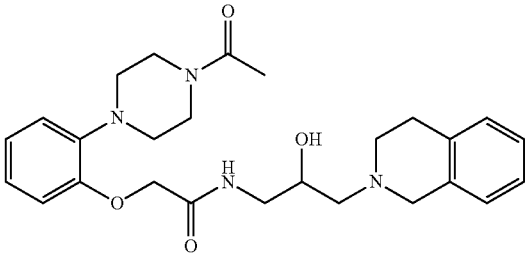
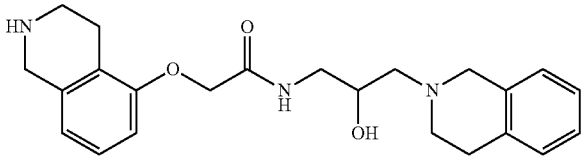
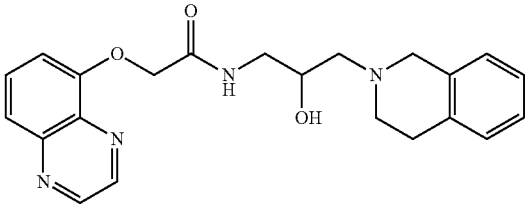
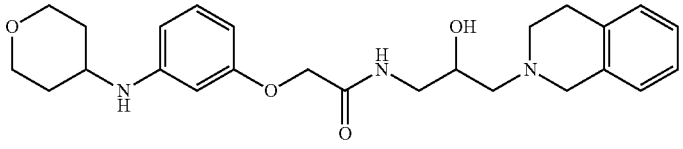
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
88		427.2471	428.1
89		427.2471	428.2
90		466.258	467.2
91		395.2209	396.1
92		392.1848	393.2
93		439.2471	440.2

TABLE 1-continued

Exemplary Compounds

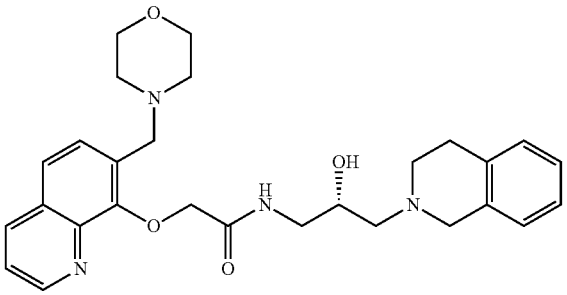
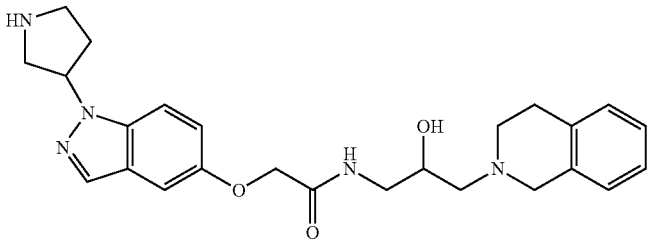
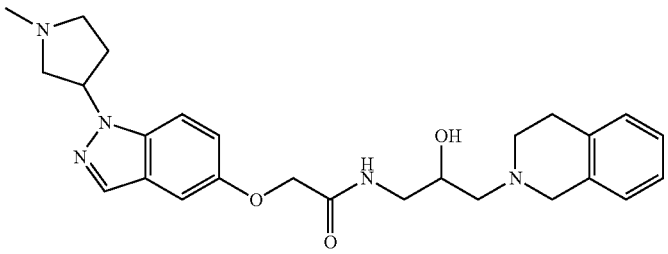
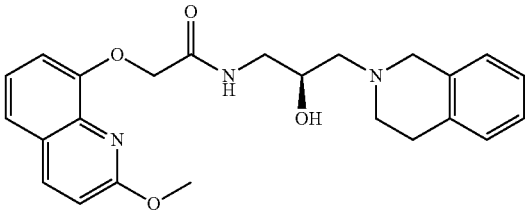
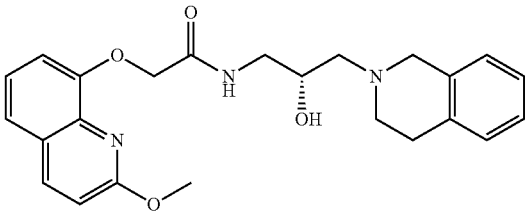
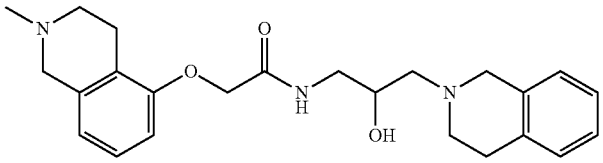
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
94		490.258	491.2
95		449.2427	450.2
96		463.2583	464.2
97		421.2002	422.2
98		421.2002	422.2
99		409.2365	410.2

TABLE 1-continued

Exemplary Compounds

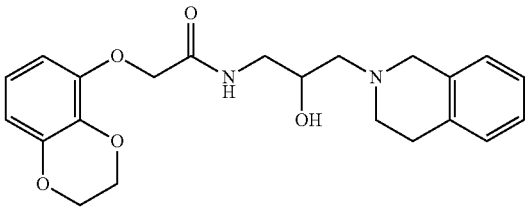
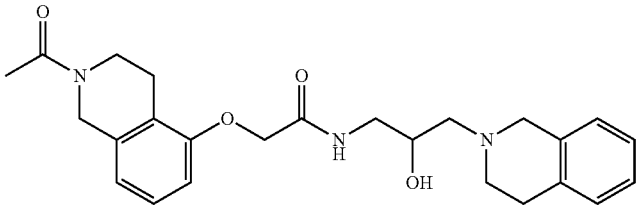
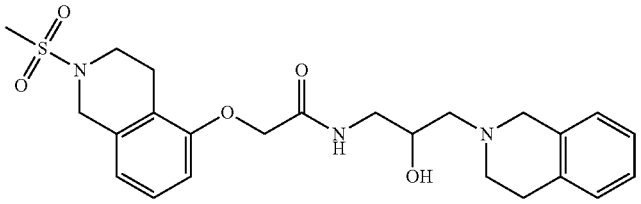
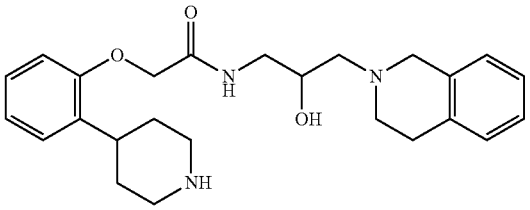
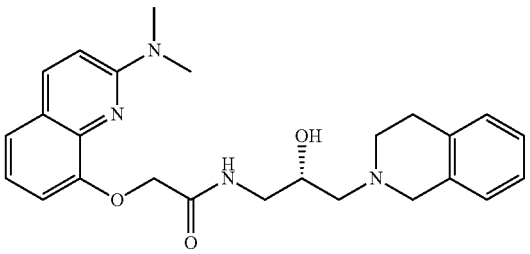
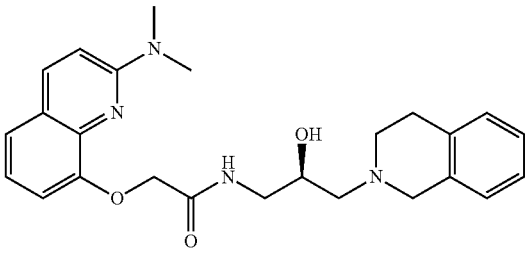
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
100		398.1842	399.1
101		437.2315	438.2
102		473.1984	474.2
103		423.2522	424.3
104		434.2318	435.2
105		434.2318	435.2

TABLE 1-continued

Exemplary Compounds

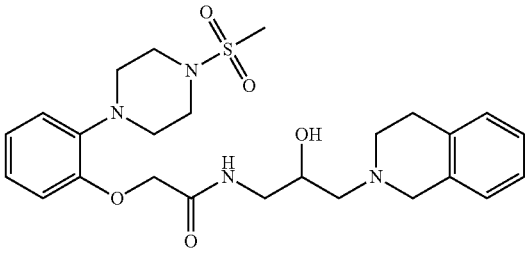
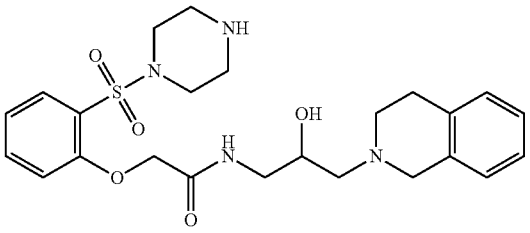
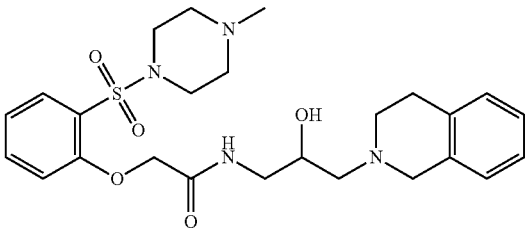
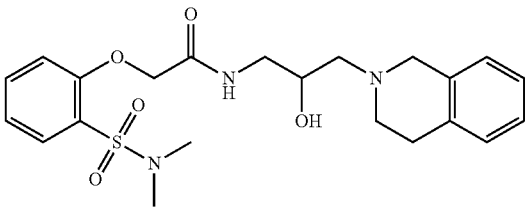
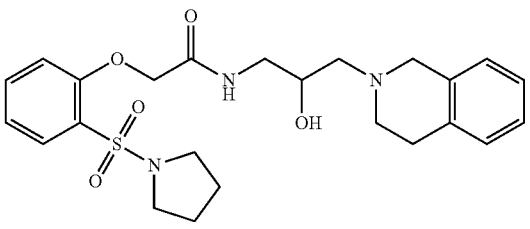
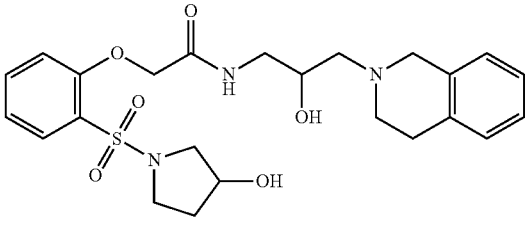
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
106		502.225	503.2
107		488.2093	489.2
108		502.225	503.2
109		447.1828	448.1
110		473.1984	474.1
111		489.1934	490.1

TABLE 1-continued

Exemplary Compounds

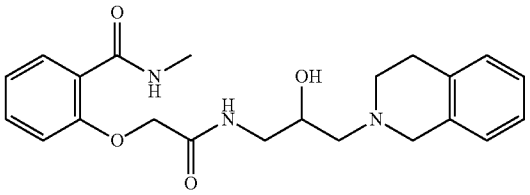
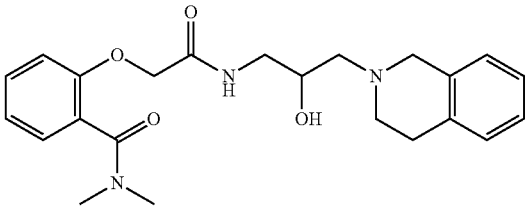
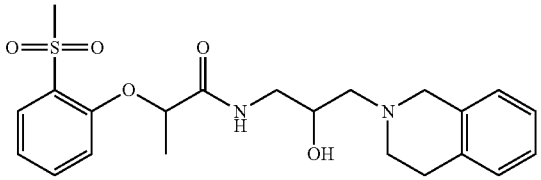
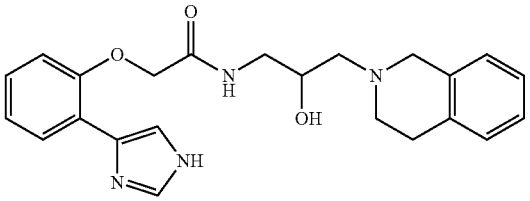
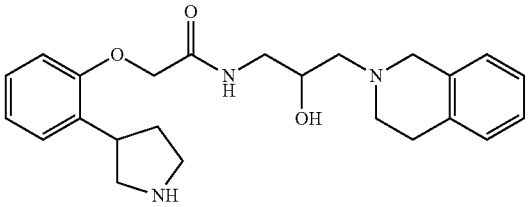
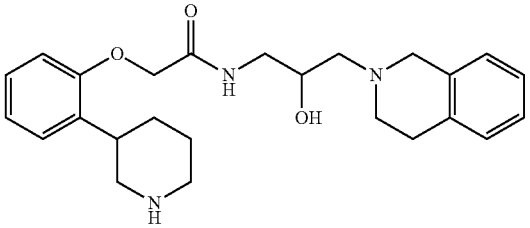
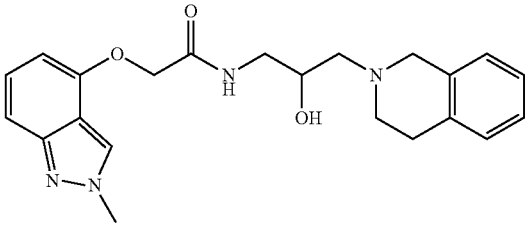
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
112		397.2002	398.2
113		411.2158	412.2
114		432.1719	433.1
115		406.2005	407.1
116		409.2365	410.2
117		423.2522	424.2
118		394.2005	395.2

TABLE 1-continued

Exemplary Compounds

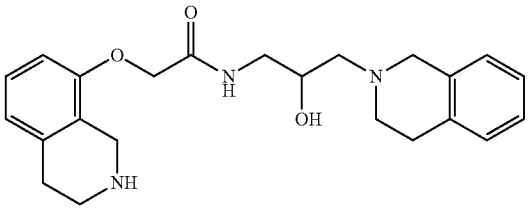
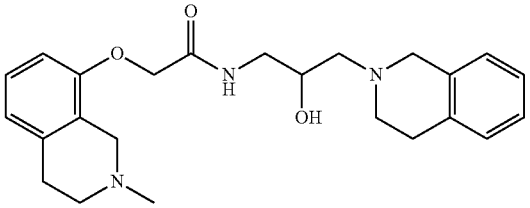
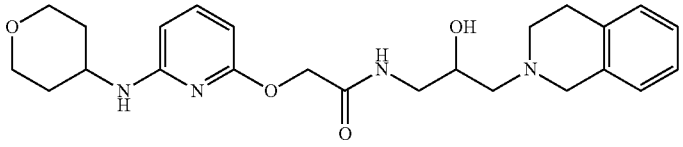
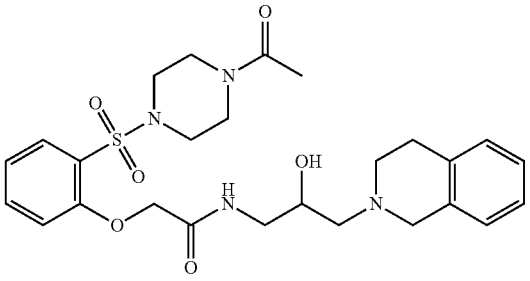
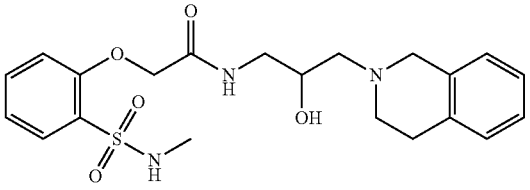
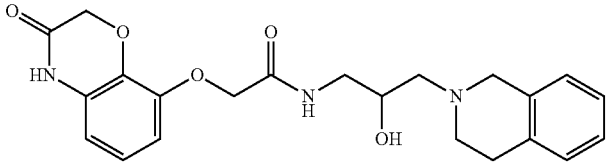
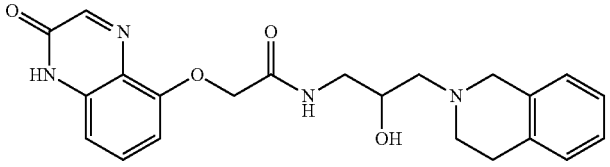
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
119		395.2209	396.1
120		409.2365	410.2
121		440.2424	441.2
122		530.2199	531.2
123		433.1671	434.1
124		411.1794	412.2
125		408.1798	409.2

TABLE 1-continued

Exemplary Compounds

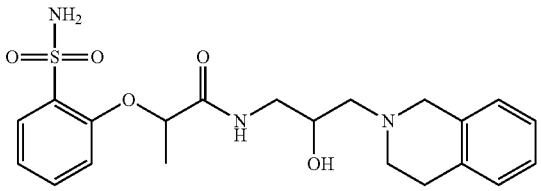
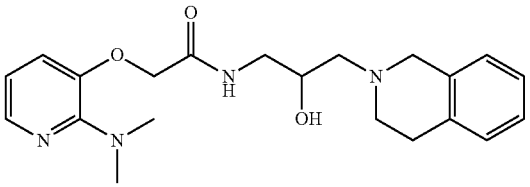
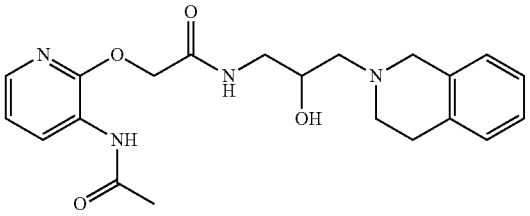
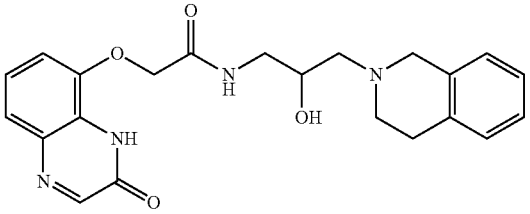
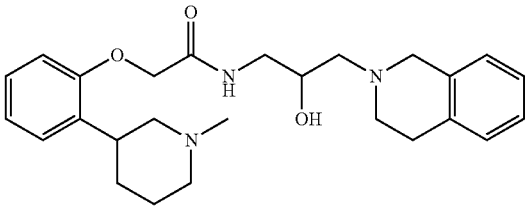
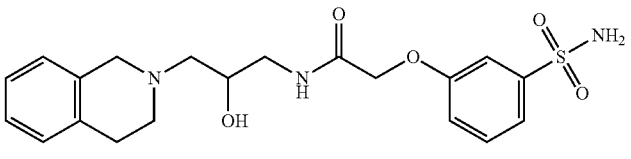
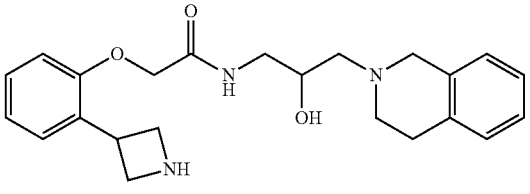
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
126		433.1671	434.1
127		384.2161	385.1
128		398.1954	399.1
129		408.1798	409.1
130		437.2678	438.3
131		419.1515	420.1
132		395.2209	396.2

TABLE 1-continued

Exemplary Compounds

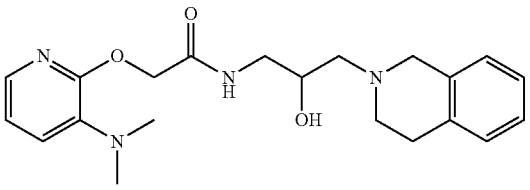
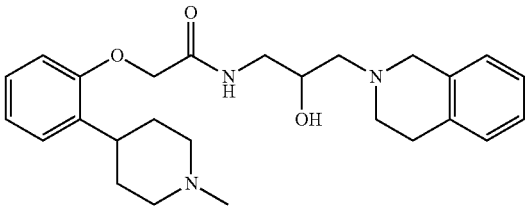
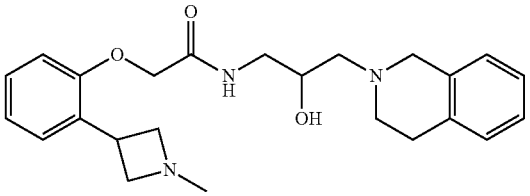
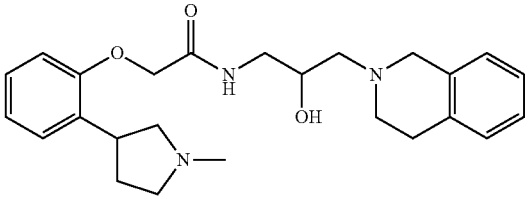
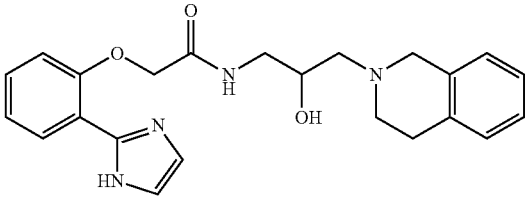
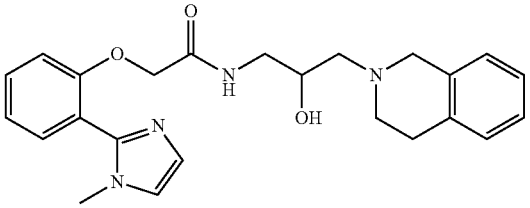
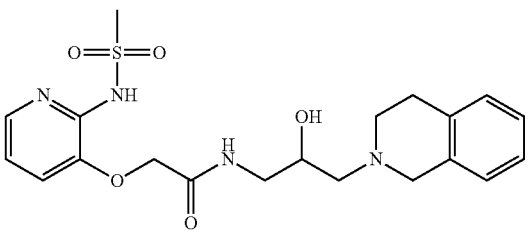
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
133		384.2161	385.2
134		437.2678	438.3
135		409.2365	410.3
136		423.2522	424.2
137		406.2005	407.1
138		420.2161	421.1
139		434.1624	435.1

TABLE 1-continued

Exemplary Compounds

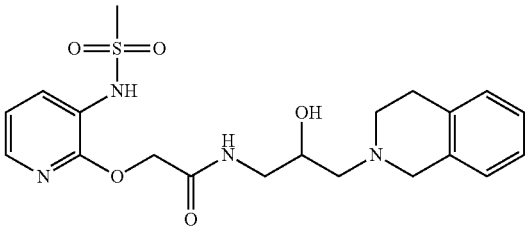
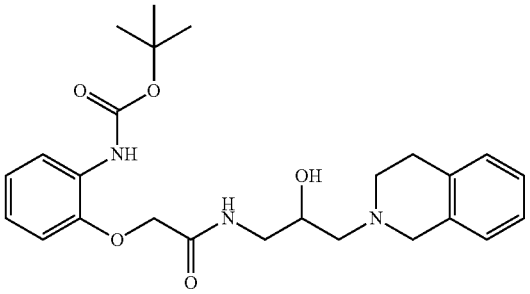
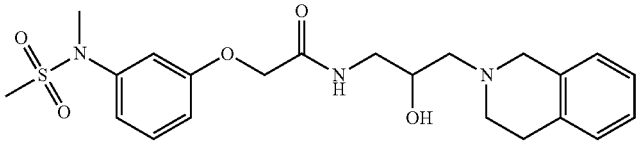
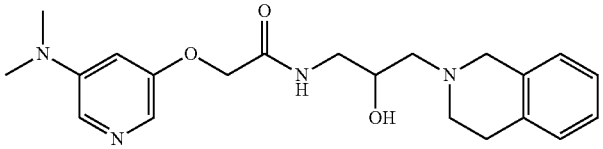
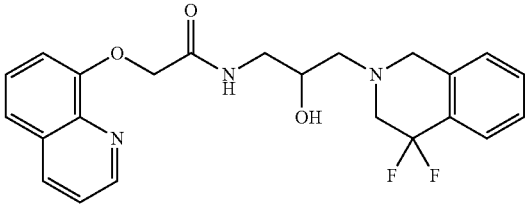
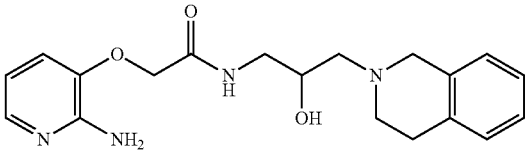
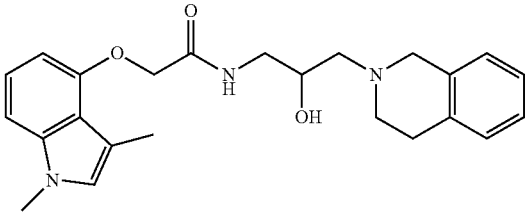
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
140		434.1624	435.1
141		455.242	456.2
142		447.1828	448.2
143		384.2161	385.2
144		427.1707	428.2
145		356.1848	357.1
146		407.2209	408.2

TABLE 1-continued

Exemplary Compounds

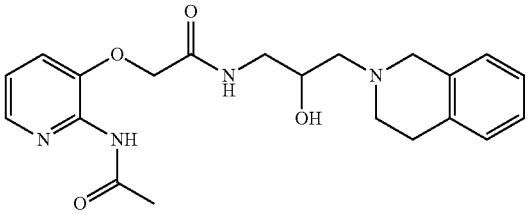
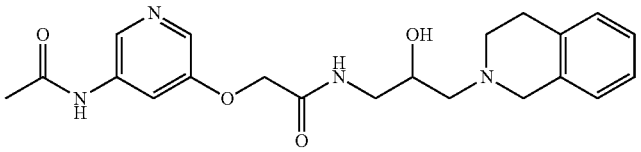
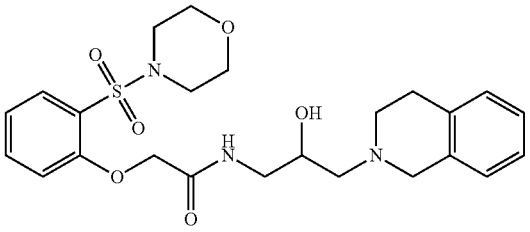
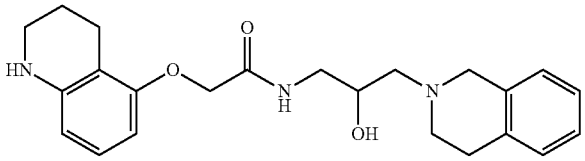
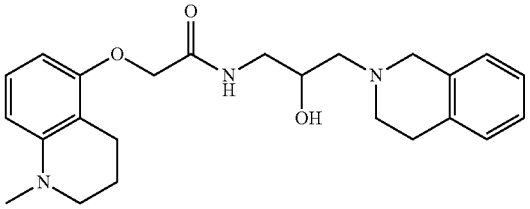
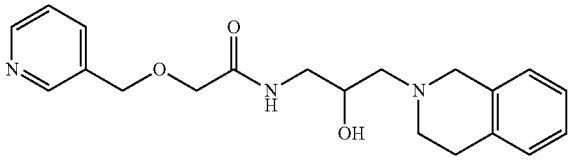
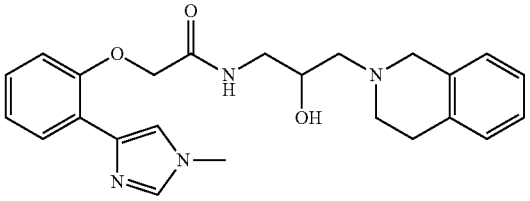
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
147		398.1954	399.2
148		398.1954	399.2
149		489.1934	490.1
150		395.2209	396.2
151		409.2365	410.2
152		355.1896	356.2
153		420.2161	421.2

TABLE 1-continued

Exemplary Compounds

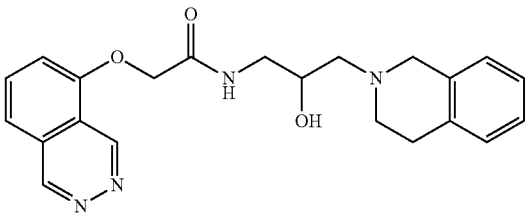
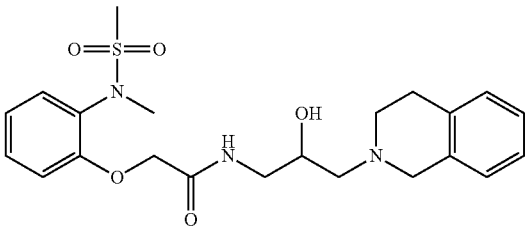
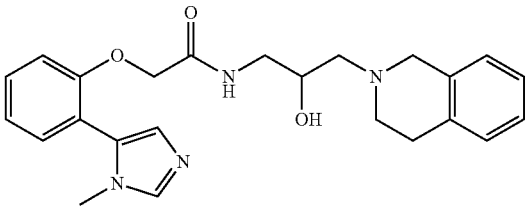
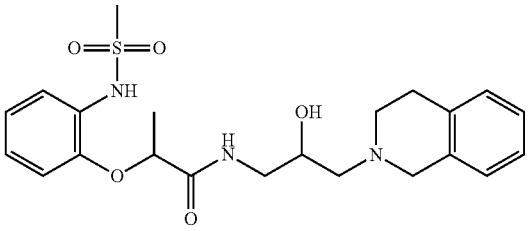
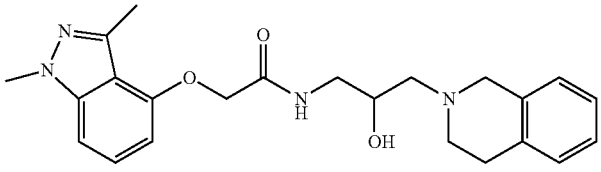
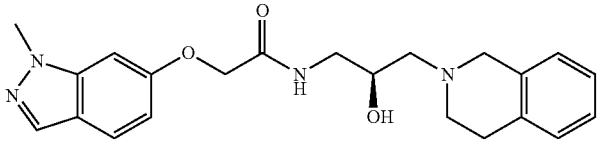
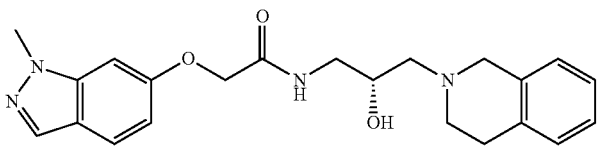
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
154		392.1848	393.2
155		447.1828	448.1
156		420.2161	421.2
157		447.1828	448.1
158		408.2161	409.2
159		394.2005	395.2
160		394.2005	395.1

TABLE 1-continued

Exemplary Compounds

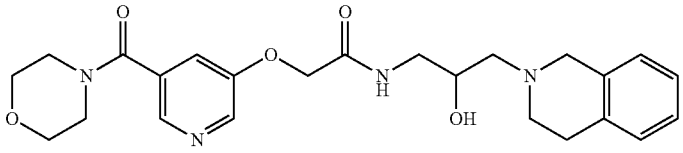
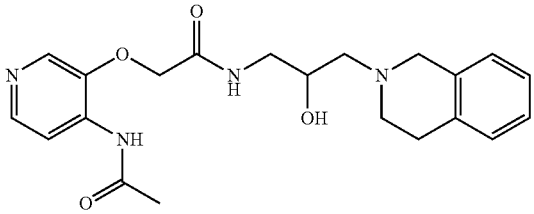
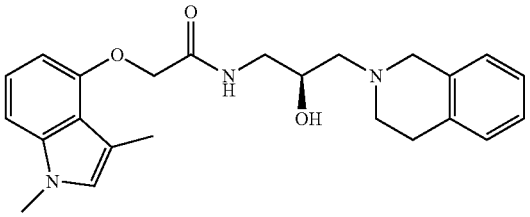
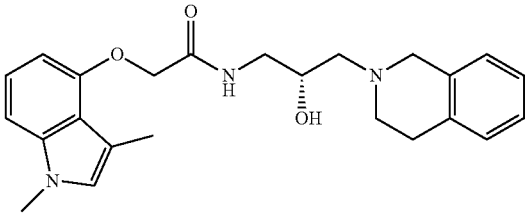
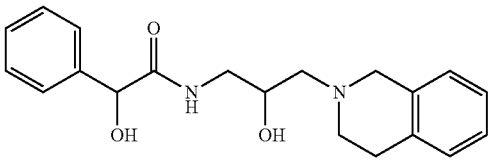
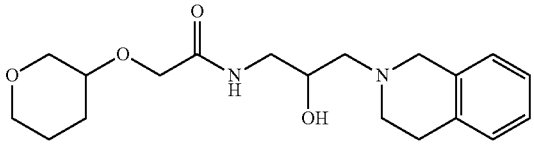
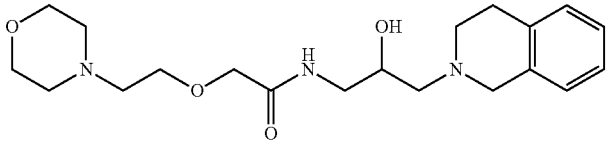
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
161		454.2216	455.2
162		398.1954	399.2
163		407.2209	408.2
164		407.2209	408.2
165		340.1787	341.1
166		348.2049	349.1
167		377.2315	378.2

TABLE 1-continued

Exemplary Compounds

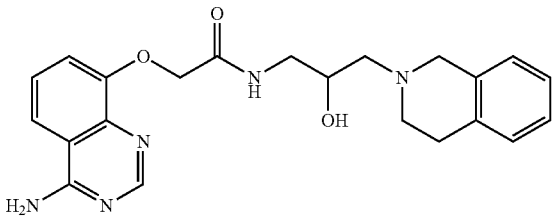
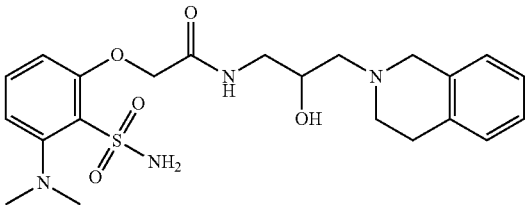
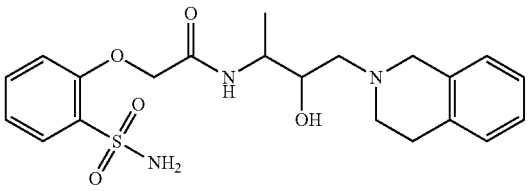
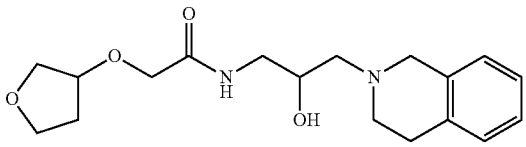
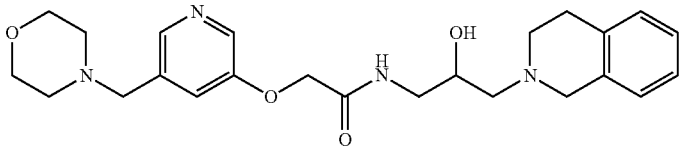
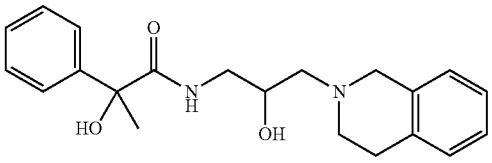
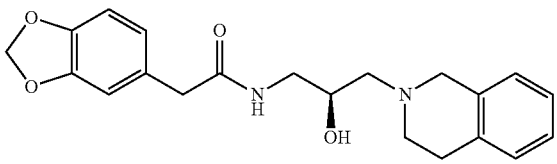
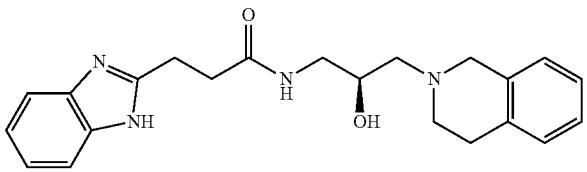
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
168		407.1957	408.2
169		462.1937	463.1
170		433.1671	434.1
171		334.1893	335.1
172		440.2424	441.2
173		354.1943	355.1
174		368.1736	369.2
175		378.2056	379.1

TABLE 1-continued

Exemplary Compounds

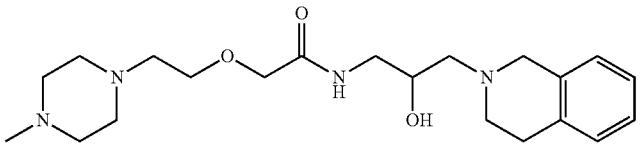
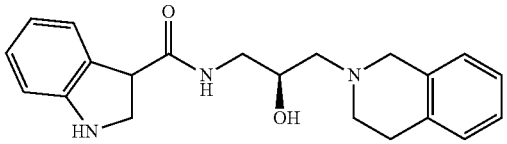
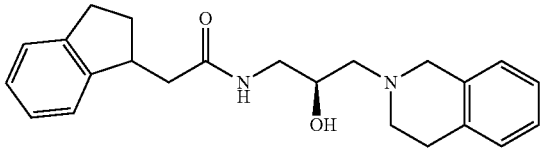
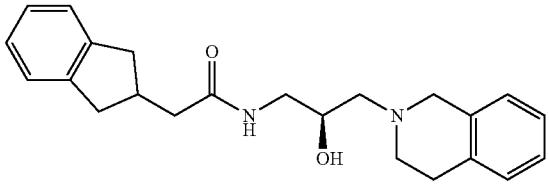
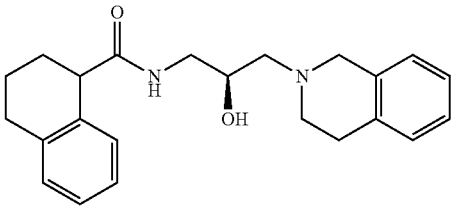
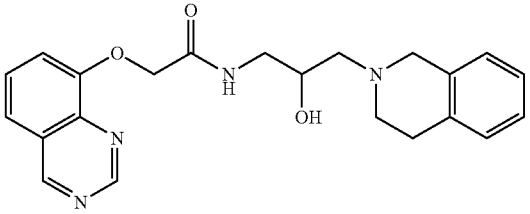
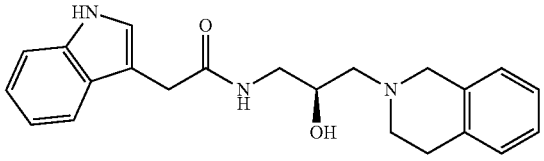
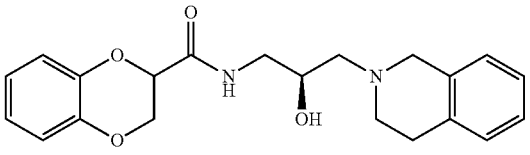
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
176		390.2631	391.1
177		351.1947	352.1
178		364.2151	365.1
179		364.2151	365.1
180		364.2151	365.1
181		392.1848	393.2
182		363.1947	364.1
183		368.1736	369.2

TABLE 1-continued

Exemplary Compounds

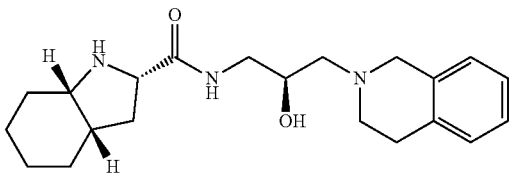
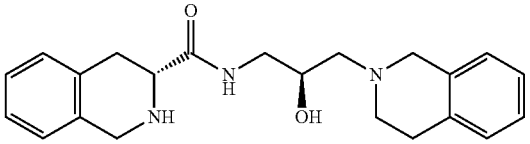
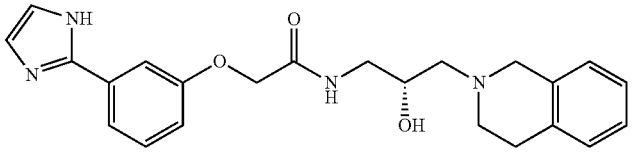
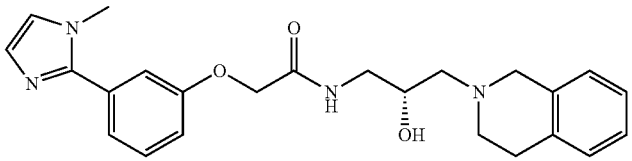
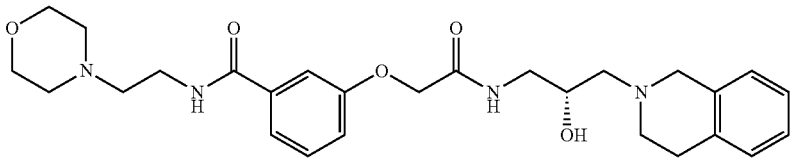
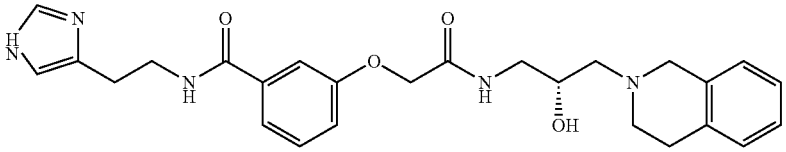
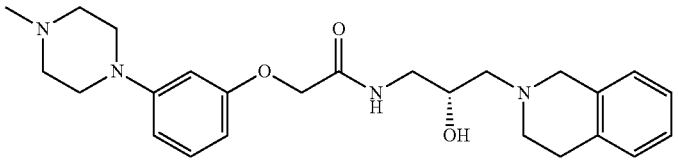
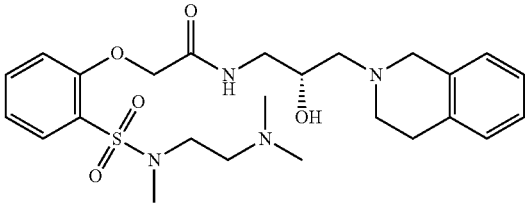
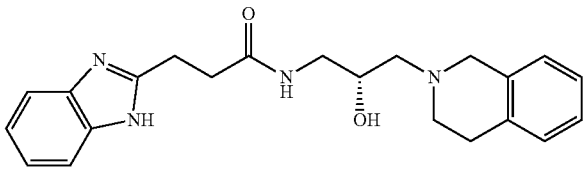
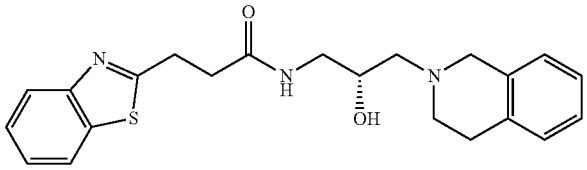
Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
184		357.2416	358.1
185		365.2103	366.1
186		406.2005	407.1
187		420.2161	421.1
188		496.2686	497.3
189		477.2376	478.3
190		438.2631	439.3
191		504.2406	505.1

TABLE 1-continued

Exemplary Compounds

Cmpd No	Structure	Exact mass	LC-MS m/z (M + H)
192		378.2056	379.1
193		395.1667	396.2

In certain embodiments, a provided compound inhibits PRMT5. In certain embodiments, a provided compound inhibits wild-type PRMT5. In certain embodiments, a provided compound inhibits a mutant PRMT5. In certain embodiments, a provided compound inhibits PRMT5, e.g., as measured in an assay described herein. In certain embodiments, the PRMT5 is from a human. In certain embodiments, a provided compound inhibits PRMT5 at an IC_{50} less than or equal to 10 μM. In certain embodiments, a provided compound inhibits PRMT5 at an IC_{50} less than or equal to 1 μM. In certain embodiments, a provided compound inhibits PRMT5 at an IC_{50} less than or equal to 0.1 μM. In certain embodiments, a provided compound inhibits PRMT5 in a cell at an EC_{50} less than or equal to 10 μM. In certain embodiments, a provided compound inhibits PRMT5 in a cell at an EC_{50} less than or equal to 1 μM. In certain embodiments, a provided compound inhibits PRMT5 in a cell at an EC_{50} less than or equal to 0.1 μM. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 10 μM. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 1 μM. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 0.1 μM. In some embodiments, a provided compound is selective for PRMT5 over other methyltransferases. In certain embodiments, a provided compound is at least about 10-fold selective, at least about 20-fold selective, at least about 30-fold selective, at least about 40-fold selective, at least about 50-fold selective, at least about 60-fold selective, at least about 70-fold selective, at least about 80-fold selective, at least about 90-fold selective, or at least about 100-fold selective for PRMT5 relative to one or more other methyltransferases.

It will be understood by one of ordinary skill in the art that the PRMT5 can be wild-type PRMT5, or any mutant or variant of PRMT5.

In certain embodiments, the PRMT5 is isoform A (GenBank accession no. NP006100) (SEQ ID NO.:1):

```
MAAMAVGGAG GSRVSSGRDL NCVPEIADTL GAVAKQGFDF
LCMPVFHPRF KREFIQEPAK NRPGPQTRSD LLLSGRDWNT
LIVGKLSPWI RPDSKVEKIR RNSEAAMLQE LNFGAYLGLP
AFLLPLNQED NTNLARVLTN HIHTGHHSSM FWMRVPLVAP
EDLRDDIIEN APTTHTEEYS GEEKTWMWWH NFRTLCDYSK
RIAVALEIGA DLPSNHVIDR WLGEPIKAAI LPTSIFLTNK
KGFPVLSKMH QRLIFRLLKL EVQFIITGTN HHSEKEFCSY
LQYLEYLSQN RPPPNAYELF AKGYEDYLQS PLQPLMDNLE
SQTYEVFEKD PIKYSQYQQA IYKCLLDRVP EEEKDTNVQV
LMVLGAGRGP LVNASLRAAK QADRRIKLYA VEKNPNAVVT
LENWQFEEWG SQVTVVSSDM REWVAPEKAD IIVSELLGSF
ADNELSPECL DGAQHFLKDD GVSIPGEYTS FLAPISSSKL
YNEVRACREK DRDPEAQFEM PYVVRLHNFH QLSAPQPCFT
FSHPNRDPMI DNNRYCTLEF PVEVNTVLHG FAGYFETVLY
QDITLSIRPE THSPGMFSWF PILFPIKQPI TVREGQTICV
RFWRCSNSKK VWYEWAVTAP VCSAIHNPTG RSYTIGL
```

In certain embodiments, the PRMT5 is isoform B (GenBank accession no. NP001034708) (SEQ ID NO.:2)

```
MRGPNSGTEK GRLVIPEKQG FDFLCMPVFH PRFKREFIQE
PAKNRPGPQT RSDLLLSGRD WNTLIVGKLS PWIRPDSKVE
KIRRNSEAAM LQELNFGAYL GLPAFLLPLN QEDNTNLARV
LTNHIHTGHH SSMFWMRVPL VAPEDLRDDI IENAPTTHTE
EYSGEEKTWM WWHNFRTLCD YSKRIAVALE IGADLPSNHV
IDRWLGEPIK AAILPTSIFL TNKKGFPVLS KMHQRLIFRL
LKLEVQFIIT GTNHHSEKEF CSYLQYLEYL SQNRPPPNAY
ELFAKGYEDY LQSPLQPLMD NLESQTYEVF EKDPIKYSQY
QQAIYKCLLD RVPEEEKDTN VQVLMVLGAG RGPLVNASLR
AAKQADRRIK LYAVEKNPNA VVTLENWQFE EWGSQVTVVS
SDMREWVAPE KADIIVSELL GSFADNELSP ECLDGAQHFL
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-continued

KDDGVSIPGE YTSFLAPISS SKLYNEVRAC REKDRDPEAQ

FEMPYVVRLH NFHQLSAPQP CFTFSHPNRD PMIDNNRYCT

LEFPVEVNTV LHGFAGYFET VLYQDITLSI RPETHSPGMF

SWFPILFPIK QPITVREGQT ICVRFWRCSN SKKVWYEWAV

TAPVCSAIHN PTGRSYTIGL

In certain embodiments, the PRMT5 is transcript variant 1 (GenBank accession no. NM_006109).

The present disclosure provides pharmaceutical compositions comprising a compound described herein, e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as described herein, and optionally a pharmaceutically acceptable excipient. It will be understood by one of ordinary skill in the art that the compounds described herein, or salts thereof, may be present in various forms, such as amorphous, hydrates, solvates, or polymorphs. In certain embodiments, a provided composition comprises two or more compounds described herein. In certain embodiments, a compound described herein, or a pharmaceutically acceptable salt thereof, is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is an amount effective for inhibiting PRMT5. In certain embodiments, the effective amount is an amount effective for treating a PRMT5-mediated disorder. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the effective amount is an amount effective to prevent a PRMT5-mediated disorder.

Pharmaceutically acceptable excipients include any and all solvents, diluents, or other liquid vehicles, dispersions, suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants, and the like, as suited to the particular dosage form desired. General considerations in formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy,* 21st Edition (Lippincott Williams & Wilkins, 2005).

Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing a compound described herein (the "active ingredient") into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the present disclosure will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

Exemplary surface active agents and/or emulsifiers include natural emulsifiers (e.g., acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g., bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (e.g., stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (e.g., carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (e.g., carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (e.g., polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan (Tween 60), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60], sorbitan tristearate (Span 65), glyceryl monooleate, sorbitan monooleate (Span 80)), polyoxyethylene esters (e.g., polyoxyethylene monostearate (Myrj 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g., Cremophor™) polyoxyethylene ethers, (e.g., polyoxyethylene lauryl ether (Brij 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F68, Poloxamer 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

Exemplary binding agents include starch (e.g., cornstarch and starch paste), gelatin, sugars (e.g., sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, etc.), natural and synthetic gums (e.g., acacia, sodium alginate,

extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (e.g., sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (e.g., citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol. Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti-oxidant. In other embodiments, the preservative is a chelating agent.

Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, *eucalyptus*, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, *litsea cubeba*, macadamia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (e.g., cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the compounds described herein are mixed with solubilizing agents such as Cremophor™, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the compounds described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may comprise buffering agents.

Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active ingredient can be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical and/or transdermal administration of a provided compound may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier and/or any desired preservatives and/or buffers as can be required. Additionally, the present disclosure encompasses the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Pat. Nos. 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Pat. Nos. 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions. Topically-administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise par-

ticles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

Low boiling propellants generally include liquid propellants having a boiling point of below 65° F. at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

Pharmaceutical compositions formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other opthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this disclosure.

Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of provided compositions will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease, disorder, or condition being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

The compounds and compositions provided herein can be administered by any route, including enteral (e.g., oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (e.g., systemic intravenous injection), regional administration via blood and/or lymph supply, and/or direct administration to an affected site. In general the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (e.g., its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (e.g., whether the subject is able to tolerate oral administration).

The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about

1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

In certain embodiments, a compound described herein may be administered at dosage levels sufficient to deliver from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

In some embodiments, a compound described herein is administered one or more times per day, for multiple days. In some embodiments, the dosing regimen is continued for days, weeks, months, or years.

It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional therapeutically active agents. In certain embodiments, a compound or composition provided herein is administered in combination with one or more additional therapeutically active agents that improve its bioavailability, reduce and/or modify its metabolism, inhibit its excretion, and/or modify its distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional therapeutically active agents. In certain embodiments, the additional therapeutically active agent is a compound of Formula (I). In certain embodiments, the additional therapeutically active agent is not a compound of Formula (I). In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In will further be appreciated that the additional therapeutically active agent utilized in this combination can be administered together in a single composition or administered separately in different compositions. The particular combination to employ in a regimen will take into account compatibility of a provided compound with the additional therapeutically active agent and/or the desired therapeutic effect to be achieved. In general, it is expected that additional therapeutically active agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

Exemplary additional therapeutically active agents include, but are not limited to, small organic molecules such as drug compounds (e.g., compounds approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells.

Also encompassed by the present disclosure are kits (e.g., pharmaceutical packs). The kits provided may comprise a provided pharmaceutical composition or compound and a container (e.g., a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of a provided pharmaceutical composition or compound. In some embodiments, a provided pharmaceutical composition or compound provided in the container and the second container are combined to form one unit dosage form. In some embodiments, a provided kits further includes instructions for use.

Compounds and compositions described herein are generally useful for the inhibition of PRMT5. In some embodiments, methods of treating PRMT5-mediated disorder in a subject are provided which comprise administering an effective amount of a compound described herein (e.g., a compound of Formula (I)), or a pharmaceutically acceptable salt thereof), to a subject in need of treatment. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the subject is suffering from a PRMT5-mediated disorder. In certain embodiments, the subject is susceptible to a PRMT5-mediated disorder.

As used herein, the term "PRMT5-mediated disorder" means any disease, disorder, or other pathological condition in which PRMT5 is known to play a role. Accordingly, in some embodiments, the present disclosure relates to treating or lessening the severity of one or more diseases in which PRMT5 is known to play a role.

In some embodiments, the present disclosure provides a method of inhibiting PRMT5 comprising contacting PRMT5 with an effective amount of a compound described herein (e.g., a compound of Formula (I)), or a pharmaceutically acceptable salt thereof. The PRMT5 may be purified or crude, and may be present in a cell, tissue, or subject. Thus, such methods encompass both inhibition of in vitro and in vivo PRMT5 activity. In certain embodiments, the method is an in vitro method, e.g., such as an assay method. It will be understood by one of ordinary skill in the art that inhibition of PRMT5 does not necessarily require that all of the PRMT5 be occupied by an inhibitor at once. Exemplary levels of inhibition of PRMT5 include at least 10% inhibition, about 10% to about 25% inhibition, about 25% to about 50% inhibition, about 50% to about 75% inhibition, at least 50% inhibition, at least 75% inhibition, about 80% inhibition, about 90% inhibition, and greater than 90% inhibition.

In some embodiments, provided is a method of inhibiting PRMT5 activity in a subject in need thereof comprising administering to the subject an effective amount of a compound described herein (e.g., a compound of Formula (I)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

In certain embodiments, provided is a method of altering gene expression in a cell which comprises contacting a cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the cell in culture in vitro. In certain embodiments, the cell is in an animal, e.g., a human. In certain embodiments, the cell is in a subject in need of treatment.

In certain embodiments, provided is a method of altering transcription in a cell which comprises contacting a cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the cell in culture in vitro. In certain embodiments, the cell is in an animal, e.g., a human. In certain embodiments, the cell is in a subject in need of treatment.

In certain embodiments, a method is provided of selecting a therapy for a subject having a disease associated with PRMT5-mediated disorder or mutation comprising the steps of determining the presence of PRMT5-mediated disorder or gene mutation in the PRMT5 gene or and selecting, based on the presence of PRMT5-mediated disorder a gene mutation in the PRMT5 gene a therapy that includes the administration of a provided compound. In certain embodiments, the disease is cancer.

In certain embodiments, a method of treatment is provided for a subject in need thereof comprising the steps of determining the presence of PRMT5-mediated disorder or a gene mutation in the PRMT5 gene and treating the subject in need thereof, based on the presence of a PRMT5-mediated disorder or gene mutation in the PRMT5 gene with a therapy that includes the administration of a provided compound. In certain embodiments, the subject is a cancer patient.

In some embodiments, a provided compound is useful in treating a proliferative disorder, such as cancer, a benign neoplasm, an autoimmune disease, or an inflammatory disease. For example, while not being bound to any particular mechanism, PRMT5 has been shown to be involved in cyclin D1 dysregulated cancers. Increased PRMT5 activity mediates key events associated with cyclin D1-dependent neoplastic growth including CUL4 repression, CDT1 overexpression, and DNA re-replication. Further, human cancers harboring mutations in Fbx4, the cyclin D1 E3 ligase, exhibit nuclear cyclin D1 accumulation and increased PRMT5 activity (Aggarwal et al., *Cancer Cell.* 2010 18(4):329-40). Additionally, PRMT5 has also been implicated in accelerating cell cycle progression through G1 phase and modulating regulators of G1; for example, PRMT5 may upregulate cyclin-dependent kinase (CDK) 4, CDK6, and cyclins D1, D2 and E1. Moreover, PRMT5 may activate phosphoinositide 3-kinase (PI3K)/AKT signaling (Wei et al., *Cancer Sci.* 2012 103(9):1640-50). Thus in some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating the following non-limiting list of cancers: breast cancer, esophageal cancer, bladder cancer, lung cancer, hematopoietic cancer, lymphoma, medulloblastoma, rectum adenocarcinoma, colon adenocarcinoma, gastric cancer, pancreatic cancer, liver cancer, adenoid cystic carcinoma, lung adenocarcinoma, head and neck squamous cell carcinoma, brain tumors, hepatocellular carcinoma, renal cell carcinoma, melanoma, oligodendroglioma, ovarian clear cell carcinoma, and ovarian serous cystadenocarcinoma.

In some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating prostate cancer and lung cancer, in which PRMT5 has been shown to play a role (Gu et al., *PLoS One* 2012; 7(8):e44033; Gu et al., *Biochem. J.* (2012) 446 (235-241)). In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of cancer. In some embodiments, a provided compound is administered in combination with other compounds, drugs, or therapeutics to treat cancer.

In some embodiments, compounds described herein are useful for treating a cancer including, but not limited to, acoustic neuroma, adenocarcinoma, adrenal gland cancer, anal cancer, angiosarcoma (e.g., lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma), appendix cancer, benign monoclonal gammopathy, biliary cancer (e.g., cholangiocarcinoma), bladder cancer, breast cancer (e.g., adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast), brain cancer (e.g., meningioma; glioma, e.g., astrocytoma, oligodendroglioma; medulloblastoma), bronchus cancer, carcinoid tumor, cervical cancer (e.g., cervical adenocarcinoma), choriocarcinoma, chordoma, craniopharyngioma, colorectal cancer (e.g., colon cancer, rectal cancer, colorectal adenocarcinoma), epithelial carcinoma, ependymoma, endotheliosarcoma (e.g., Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma), endometrial cancer (e.g., uterine cancer, uterine sarcoma), esophageal cancer (e.g., adenocarcinoma of the esophagus, Barrett's adenocarinoma), Ewing sarcoma, eye cancer (e.g., intraocular melanoma, retinoblastoma), familiar hypereosinophilia, gall bladder cancer, gastric cancer (e.g., stomach adenocarcinoma), gastrointestinal stromal tumor (GIST), head and neck cancer (e.g., head and neck squamous cell carcinoma, oral cancer (e.g., oral squamous cell carcinoma (OSCC), throat cancer (e.g., laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)), hematopoietic cancers (e.g., leukemia such as acute lymphocytic leukemia (ALL) (e.g., B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (e.g., B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (e.g., B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (e.g., B-cell CLL, T-cell CLL); lymphoma such as Hodgkin lymphoma (HL) (e.g., B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (e.g., B-cell NHL such as diffuse large cell lymphoma (DLCL) (e.g., diffuse large B-cell lymphoma (DLBCL)), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (e.g., mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (i.e., "Waldenstrom's macroglobulinemia"), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (e.g., cutaneous T-cell lymphoma (CTCL) (e.g., mycosis fungiodes, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (e.g., alpha chain disease, gamma chain disease, mu chain disease), hemangioblastoma, inflammatory myofibroblastic tumors, immunocytic amyloidosis, kidney cancer (e.g., nephroblastoma a.k.a. Wilms' tumor, renal cell carcinoma), liver cancer (e.g., hepatocellular cancer (HCC), malignant hepatoma), lung cancer (e.g., bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung), leiomyosarcoma (LMS), mastocytosis (e.g., systemic mastocytosis), myelodysplastic syndrome (MDS), mesothelioma, myeloproliferative disorder (MPD) (e.g., polycythemia Vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) a.k.a. myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)), neuroblastoma, neurofibroma (e.g., neurofibromatosis (NF) type 1 or type 2, schwannomatosis), neuroendocrine cancer (e.g., gastroenteropancreatic neuroendoctrine tumor (GEP-NET), carcinoid tumor), osteosarcoma, ovarian cancer (e.g., cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma), papillary adenocarcinoma, pancreatic cancer (e.g., pancreatic andenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors), penile cancer (e.g., Paget's disease of the penis and scrotum), pinealoma, primitive

neuroectodermal tumor (PNT), prostate cancer (e.g., prostate adenocarcinoma), rectal cancer, rhabdomyosarcoma, salivary gland cancer, skin cancer (e.g., squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)), small bowel cancer (e.g., appendix cancer), soft tissue sarcoma (e.g., malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma), sebaceous gland carcinoma, sweat gland carcinoma, synovioma, testicular cancer (e.g., seminoma, testicular embryonal carcinoma), thyroid cancer (e.g., papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer), urethral cancer, vaginal cancer and vulvar cancer (e.g., Paget's disease of the vulva).

In some embodiments, a provided compound is useful in treating a metabolic disorder, such as diabetes or obesity. For example, while not being bound to any particular mechanism, a role for PRMT5 has been recognized in adipogenesis. Inhibition of PRMT5 expression in multiple cell culture models for adipogenesis prevented the activation of adipogenic genes, while overexpression of PRMT5 enhanced adipogenic gene expression and differentiation (LeBlanc et al., *Mol Endocrinol.* 2012 April; 26(4):583-97). Additionally, it has been shown that adipogenesis plays a pivotal role in the etiology and progression of diabetes and obesity (Camp et al., *Trends Mol Med.* 2002 September; 8(9):442-7). Thus in some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating diabetes and/or obesity.

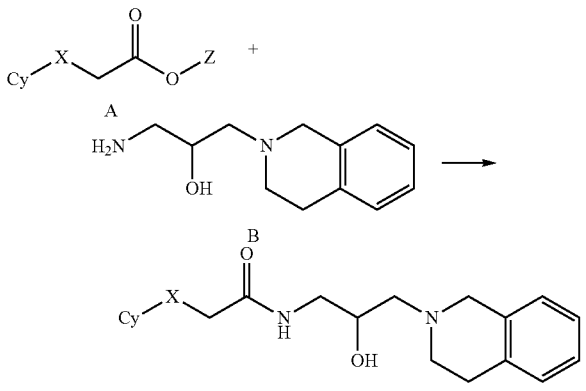
In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, diabetes. In some embodiments, the diabetes is Type 1 diabetes. In some embodiments, the diabetes is Type 2 diabetes. In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, obesity. In some embodiments, a provided compound is useful to make a subject lose weight. In some embodiments, a provided compound could be used in combination with other compounds, drugs, or therapeutics, such as metformin and insulin, to treat diabetes and/or obesity.

In some embodiments, a provided compound is useful in treating a blood disorder, e.g., a hemoglobinopathy, such as sickle cell disease or β-thalassemia. For example, while not being bound to any particular mechanism, PRMT5 is a known repressor of γ-globin gene expression, and increased fetal γ-globin (HbF) levels in adulthood are associated with symptomatic amelioration in sickle cell disease and β-thalassemia (Xu et al., *Haematologica.* 2012 November; 97(11):1632-40). Thus in some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating a blood disorder, such as a hemoglobinopathy such as sickle cell disease or β-thalassemia.

In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, sickle cell disease. In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, β-thalassemia. In some embodiments, a provided compound could be used in combination with other compounds, drugs, or therapeutics, to treat a hemoglobinopathy such as sickle cell disease or β-thalassemia.

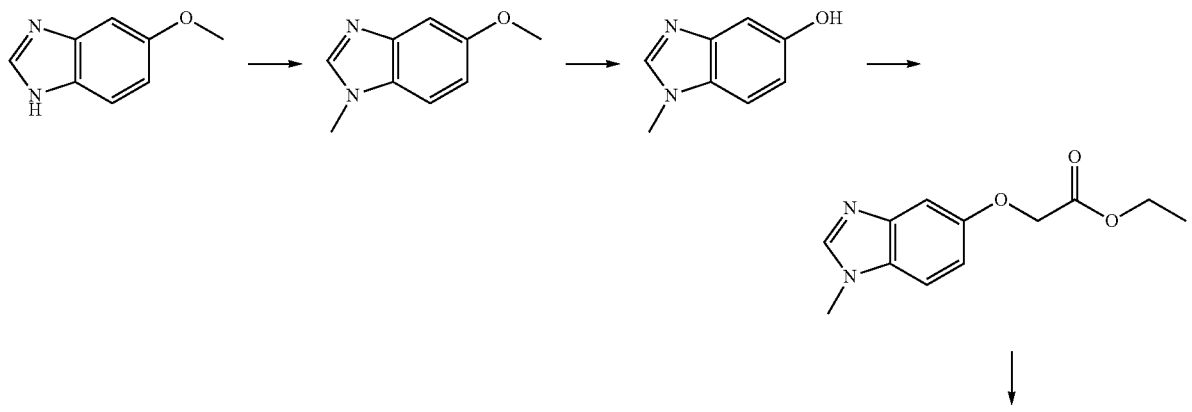
In some embodiments, compounds described herein can prepared using methods shown in general Scheme 1. Compound B can be prepared via ring opening of a chiral or racemic epoxide group. This amino alcohol intermediate can be coupled to form an amide via normal amide coupling methodology using a carboxylic acid A wherein Z is hydrogen or via amination of an ester of intermediate A when Z is an optionally substituted aliphatic group.

Scheme 1



For example, exemplary Schemes 2 and 3 show such couplings.

Scheme 2



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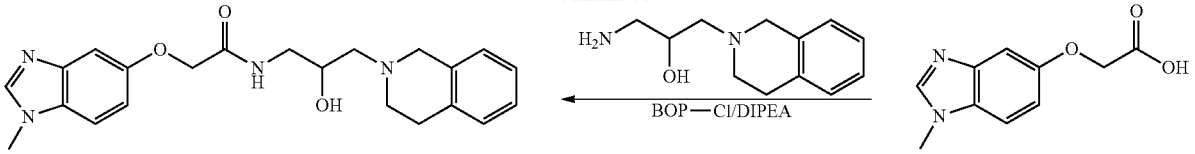
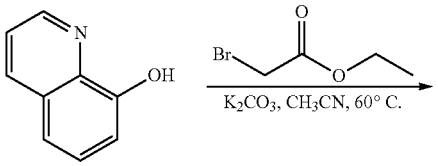


Scheme 3



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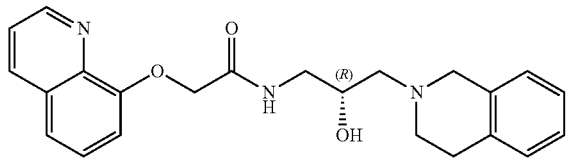
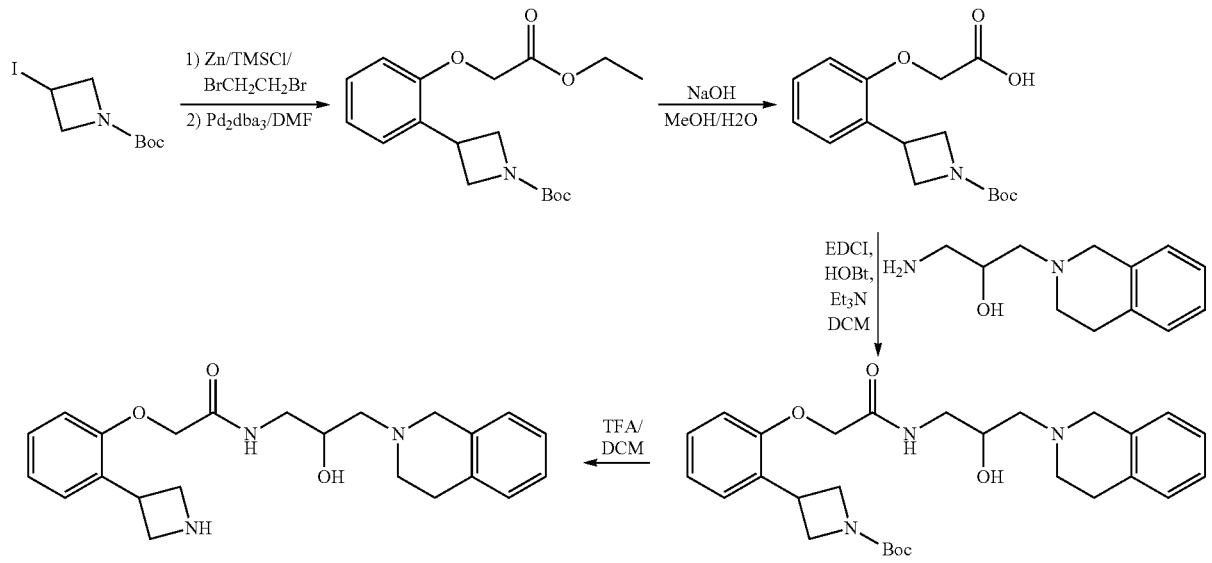


In some embodiments, an amide coupling step can be used to provide a key intermediate for further synthesis, as shown, for example, in exemplary Scheme 4.

Scheme 4



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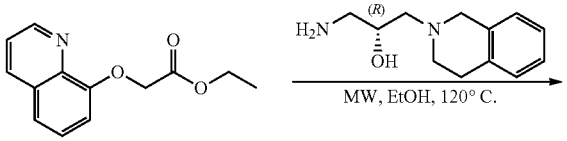


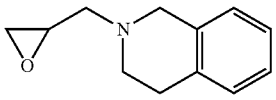
EXAMPLES

In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

Synthetic Methods

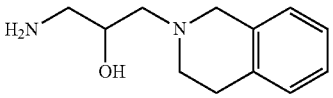
Intermediate Synthesis

2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline



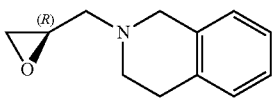
To a solution of 1,2,3,4-tetrahydroisoquinoline (15 g, 0.11 mol) in MeCN (100 mL) was added K_2CO_3 (30.7 g, 0.23 mol) at 0° C. 2-(bromomethyl)oxirane (17 g, 0.12 mol) was added to the reaction after 1 h. The solution was stirred at 22° C. for 16 h at which time the solids were filtered and washed with MeCN. The solution was concentrated and the residue was used in the next step without further purification (17 g, Yield 78%). LCMS (m/z): 190.1 (M+1).

1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol



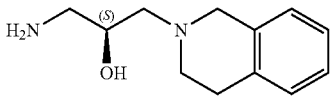
To a solution of 2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (17 g, 0.09 mol) in EtOH (300 mL) at −78° C. was slowly bubbled NH_3 (g). The reaction reaction was then sealed and heated at 80° C. for 3 h. The reaction mixture was concentrated and the crude product was used in next step without further purification (18 g, Yield 96%). LCMS (m/z): 207.1 (M+1).

(R)-2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline



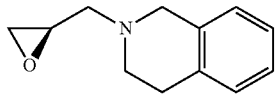
To a solution of 1,2,3,4-tetrahydroisoquinoline (10 g, 0.15 mol) in THF (100 mL) at 0° C. was added KF (22 g, 0.3 mmol). After 1 h, (S)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (21.4 g, 0.17 mmol) was added and the resulting solution was stirred at 22° C. for 16 h. The solid was removed by filtration and washed with THF. The solution was concentrated and the crude compound was used for next step without further purification (15 g, Yield 53%). LCMS (m/z): 190.1 (M+1).

(S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl) propan-2-ol



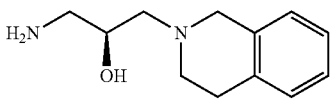
To a solution of (R)-2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (15 g, 0.08 mol) in EtOH (100 mL) at −78° C. was slowly bubbled NH_3 (g). The reaction mixture was then sealed and heated at 80° C. for 3 h. The reaction mixture was concentrated and the crude product was used in next step without further purification (15 g, Yield 92%). LCMS (m/z): 207.1 (M+1).

Alternative synthesis of (R)-2-(oxiran-2-ylmethyl)-1, 2,3,4-tetrahydroisoquinoline



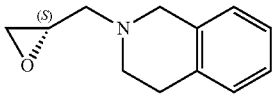
To a solution of 1,2,3,4-tetrahydroisoquinoline (1 g, 7.52 mmol) in MeOH (40 mL) was added K_2CO_3 (5.19 g, 37.6 mmol) under 0° C. After stirring for 30 minutes, (R)-2-(chloromethyl) oxirane (0.692 g, 7.52 mmol) was added the reaction. The mixture was then stirred at 0° C. overnight before filtration and washing of the solid by with MeOH. The solution was concentrated and the residue purified by column separation to give the title compound as a colorless oil (70% purity). This crude was used directly in the next step. LCMS (m/z): 190.1 (M+1).

Alternative synthesis of (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol



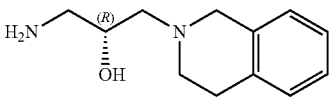
To a solution of (R)-2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (200 mg, 5.2 mmol) in EtOH (20 mL) was added NH_4OH (600 mg, 35.2 mmol) at −78° C. The reaction mixture was then warmed and heated at 100° C. for 3 h in a seal tube. The reaction mixture was concentrated and the crude product was used in next step without further purification. LCMS (m/z): 207.1 (M+1).

(S)-2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline



To a solution of 1,2,3,4-tetrahydroisoquinoline (5 g, 7.52 mmol) in THF (100 mL) was added KF (8.57 g, 150.4 mmol) at 0° C. (R)-oxiran-2-ylmethyl3-nitrobenzenesulfonate (10.7 g, 41.4 mmol) was added to the reaction in 1 h. The solution was stirred at room temperature overnight. The solid was removed by filtration and washed with THF. The solution was then concentrated and the residue used for next step without further purification (11.3 g Yield 80%). LCMS (m/z): 190.1 (M+1).

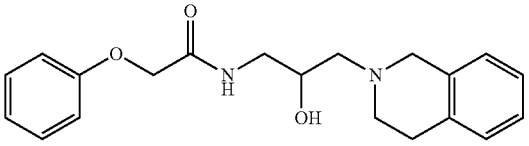
(R)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl) propan-2-ol



To a solution of (S)-2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (2.2 g, 0.012 mol) in EtOH (30 mL), NH_3 was bubbled to the solution under −78° C. The reaction mixture was then sealed and heated at 80° C. for 3 h. After LCMS indicated completion of the reaction, the mixture was concentrated and the crude product was used in next step without further purification (2.2 g, Yield 90%). LCMS (m/z): 207.1 (M+1).

Compound 1

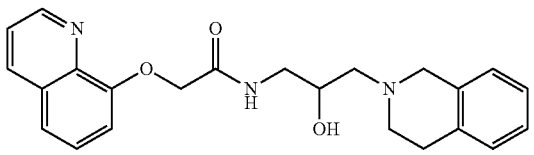
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-phenoxyacetamide



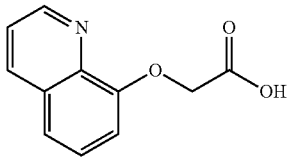
To a stirred mixture of 2-phenoxyacetic acid (100 mg, 0.658 mmol) in DCM (10 mL) was added TEA (200 mg, 1.98 mmol), 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (135 mg, 0.658 mmol) and HATU (250 mg, 0.658 mmol). The mixture was stirred at 25° C. for 16 hours then quenched with water (20 mL) and extracted with DCM (3×20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was then purified by prep-HPLC to afford the title compound (76 mg, 34% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.27 (m, 2H), 7.14-7.08 (m, 3H), 7.05-6.98 (m, 2H), 6.93 (d, J=8.0 Hz, 2H), 4.54 (s, 2H), 4.55-4.52 (m, 1H), 4.42 (s, 2H), 4.06-4.00 (m, 1H), 3.71 (s, 2H), 3.48-3.38 (m, 2H), 2.91 (d, J=5.6 Hz, 2H), 2.84 (d, J=5.6 Hz, 2H), 2.60 (d, J=6.8 Hz, 2H) ppm. LCMS (m/z): 341.2 $[M+H]^+$.

Compound 6

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(quinolin-8-yloxy)acetamide

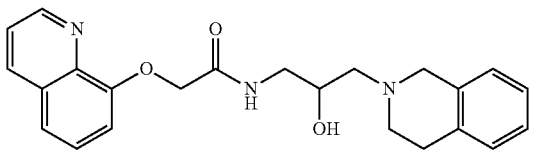


Step 1: 2-(quinolin-8-yloxy)acetic acid



To a stirred mixture of quinolin-8-ol (500 mg, 3.45 mmol) in MeCN (5 mL) was added ethyl bromoacetate (687 mg, 4.14 mmol) and K_2CO_3 (952 mg, 6.90 mmol). The mixture was stirred at 80° C. for 4 hours until TLC analysis showed completion of the reaction. The mixture was filtered and the filtrate concentrated. NaOH (276 mg, 6.90 mmol) and water: EtOH (1:1, 10 mL) was then added to the residue and the resulting mixture stirred at 50° C. for 4 hours. After cooling, the mixture was acidified by addition of 1M HCl to pH 3 and then extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated to yield the crude target product which was used directly for the next step.

Step 2: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(quinolin-8-yloxy)acetamide

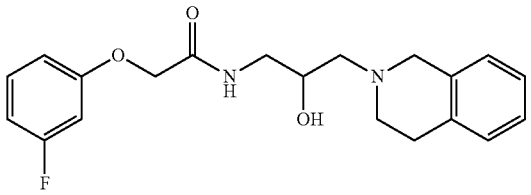


To a stirred mixture of 2-(quinolin-8-yloxy)acetic acid (100 mg, 0.492 mmol) in DMF (5 mL) was added DIEA (95 mg, 0.738 mmol), 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (100 mg, 0.492 mmol) and BOP-Cl (151 mg, 0.591 mmol). The mixture was stirred at 25° C. for 48 hours then the reaction mixture was quenched by addition of water (20 mL) and extracted with DCM (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was then purified by prep-HPLC to afford the desired product

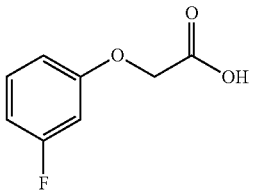
(8 mg, Yield: 4%). ^{1}H NMR (400 MHz, MeOD) δ=8.91 (d, J=4.3 Hz, 1H), 8.42 (d, J=8.3 Hz, 1H), 7.69-7.54 (m, 3H), 7.30 (d, J=7.3 Hz, 1H), 7.12-6.96 (m, 4H), 4.78 (s, 2H), 4.18-4.07 (m, 1H), 3.71 (s, 2H), 3.60-3.49 (m, 1H), 3.48-3.40 (m, 1H), 2.89 (d, J=5.8 Hz, 2H), 2.84 (d, J=4.8 Hz, 2H), 2.65-2.61 (m, 2H). LCMS (m/z): 392.2 (M+1).

Compound 7

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(3-fluorophenoxy)acetamide

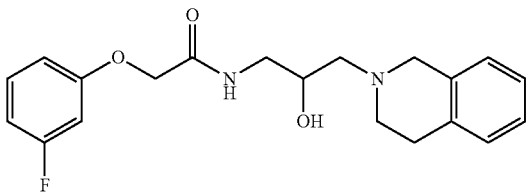


Step 1: 2-(3-fluorophenoxy)acetic acid



To a stirred mixture of 3-fluorophenol (100 mg, 0.893 mmol) in MeCN (5 mL) was added ethyl bromoacetate (222 mg, 1.34 mmol) and K_2CO_3 (369 mg, 2.68 mmol). The mixture was stirred at 80° C. for 4 hours. The mixture was then filtered and the filtrate concentrated. NaOH (71 mg, 1.79 mmol) and water:EtOH (1:1, 10 mL) was added to the residue and the mixture stirred at 50° C. for 4 hours. The mixture was acidified by adding 1M HCl, and then extracted with ethyl acetate (2×30 mL). The combined extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was directly for the next step. LCMS (m/z): 171.0 (M+1).

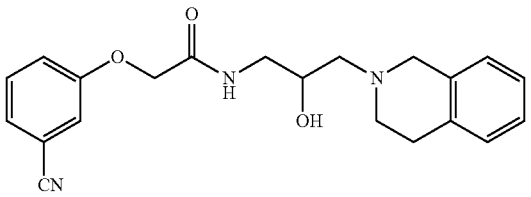
Step 2: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(3-fluorophenoxy)acetamide



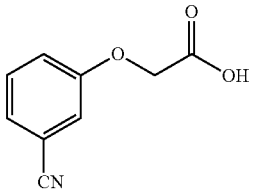
To a stirred mixture of 2-(3-fluorophenoxy)acetic acid (252 mg, 0.893 mmol) in DCM (5 mL) was added DIEA (173 mg, 1.34 mmol), 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (183 mg, 0.893 mmol), and Bop-Cl (273 mg, 1.07 mmol). The mixture was stirred at 25° C. for 16 hours then quenched with water (20 mL), extracted with DCM (3×20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was then purified by prep-HPLC to afford the product (18 mg, Yield 5.6%). ^{1}H NMR (400 MHz, METHANOL-d_4) δ=7.26-7.29 (m, 1H), 7.13-7.02 (m, 4H), 6.76-6.69 (m, 3H), 4.55 (s, 2H), 4.06-4.00 (m, 1H), 3.71 (s, 1H), 3.47-3.31 (m, 2H), 2.91-2.90 (m, 2H), 2.86-2.77 (m, 2H), 2.61 (d, J=6.0 Hz, 2H). LCMS (m/z): 359.1 (M+1).

Compound 8

2-(3-cyanophenoxy)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)acetamide

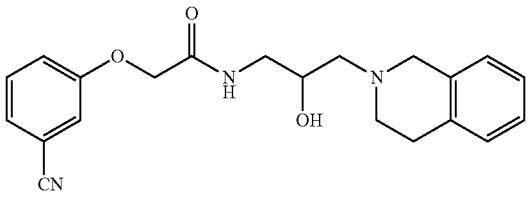


Step 1: 2-(3-cyanophenoxy) acetic acid



To a stirred mixture of 3-hydroxybenzonitrile (100 mg, 0.840 mmol) in MeCN (5 mL) was added ethyl bromoacetate (209 mg, 1.26 mmol) and K_2CO_3 (350 mg, 2.52 mmol). The mixture was stirred at 80° C. for 4 hours until TLC showed completion of the reaction. The mixture was filtered and the filtrate concentrated. NaOH (67 mg, 1.68 mmol) and water: EtOH (1:1, 10 mL) was added to the residue and the mixture stirred at 50° C. for 4 hours. After cooling, the mixture was acidified by 1M HCl, extracted with ethyl acetate (2×30 mL). The combined extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was used directly in the next step. LCMS (m/z): 178.0 (M+1).

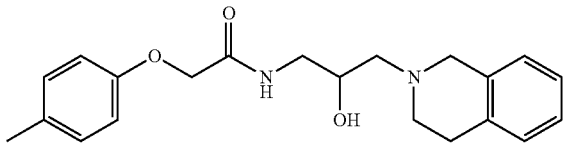
Step 2: 2-(3-cyanophenoxy)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)acetamide



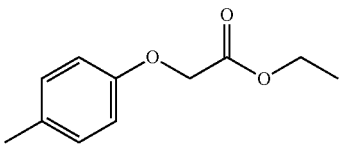
To a stirred mixture of 2-(3-cyanophenoxy) acetic acid (100 mg, 0.565 mmol) in DCM (5 mL) was added DIEA (109 mg, 0.85 mmol), 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (116 mg, 0.565 mmol) and BopCl (173 mg, 0.678 mmol). The resulting mixture was stirred at 25° C. for 16 hours until LCMS showed the completion of the reaction. The reaction mixture was quenched by addition of water (20 mL) then extracted with DCM (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to afford the desired final product (24 mg, Yield 12%). ^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.48 (dd, J_1=J_2=7.6 Hz, 1H), 7.37 (d, J=7.6 Hz, 1H), 7.25-7.21 (m, 2H), 7.13-7.03 (m, 4H), 4.60 (s, 2H), 4.04-4.00 (m, 1H), 3.71 (s, 2H), 3.44 (d, J=6.0 Hz, 2H), 2.93-2.80 (m, 4H), 2.62 (d, J=5.6 Hz, 2H). LCMS (m/z): 366.1 (M+1).

Compound 9

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(p-tolyloxy)acetamide

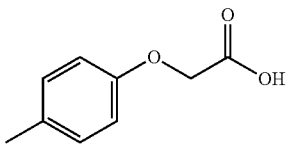


Step 1: ethyl 2-(p-tolyloxy)acetate



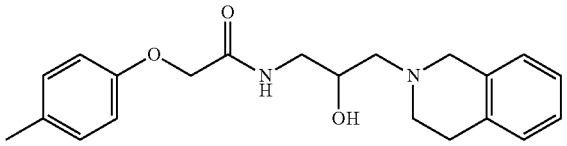
To a mixture of p-cresol (500 mg, 4.63 mmol) and ethyl 2-bromoacetate (928 mg, 5.56 mmol) in CH_3CN (10 mL) was added K_2CO_3 (3 g, 21.7 mmol). The reaction mixture was stirred at 80° C. for 4 h. The solid was removed by filtration and the filtrate was concentrated to give the title compound which was used in the next step without further purification.

Step 2: 2-(p-tolyloxy)acetic acid



To a solution of ethyl 2-(p-tolyloxy)acetate (200 mg, 1 mmol) in EtOH (10 ml) was added 10% NaOH solution (10 ml) at 26° C. The mixture was stirred for 30 min, concentrated then water (20 mL) added to it before washing with ethyl acetate (2×20 mL). The aqueous layer was acidified with 2N HCL until pH 3 and extracted with EA (2×20 ml). The organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the title compound which was used in next step without further purification.

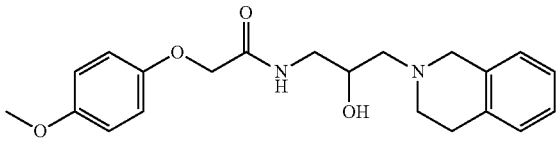
Step 3: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(p-tolyloxy)acetamide



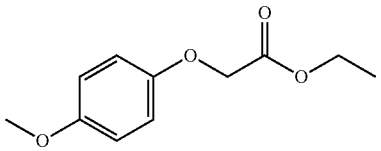
A mixture of compound 2-(p-tolyloxy)acetic acid (100 mg, 0.60 mmol), 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl) propan-2-ol (124 mg, 0.60 mmol), BOP-Cl (183 mg, 0.72 mmol) and DIPEA (1 mL) in DCM (10 mL) was stirred at room temperature for 4 h. The solvent was removed by concentration and the crude product was purified by pre-HPLC to give the title compound (27.8 mg, yield 13.1%). ^{1}H NMR (500 MHz, MeOD): δ 7.32-7.25 (m, 3H), 7.20 (d, J=7.2 Hz, 1H), 7.12 (d, J=8.4 Hz, 2H), 6.90 (d, J=8.8 Hz, 2H), 4.65-4.52 (br.s, 1H), 4.52 (s, 2H), 4.46-4.30 (br.s, 1H), 4.30-4.24 (m, 1H), 3.85-3.70 (br.s, 1H), 3.43 (d, J=5.6 Hz, 1H), 3.26-3.17 (m, 4H), 2.26 (s, 3H) ppm; ESI-MS (m/z): 355.2 $[M+1]^+$.

Compound 12

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(4-methoxyphenoxy)acetamide



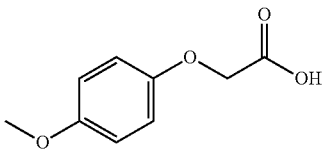
Step 1: ethyl 2-(4-methoxyphenoxy)acetate



To a solution of 4-methoxyphenol (500 mg, 4.03 mmol) in CH_3CN (10 mL) was added ethyl 2-bromo-2-methylpropanoate (807 mg, 4.84 mmol) and K_2CO_3 (3 g, 21.7 mmol) at 25° C. The mixture was refluxed for 16 h. The mixture was then diluted with water (100 mL), extracted with ethyl acetate (2×50 mL) and the combined organic layers washed with

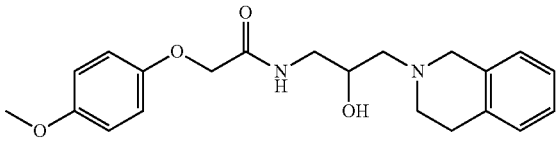
brine (30 mL), dried over Na_2SO_4 and concentrated to give the title compound which was used in next step without further purification.

Step 2: 2-(4-methoxyphenoxy)acetic acid



To a solution of ethyl 2-methyl-2-phenoxypropanoate (210 mg, 1 mmol) in EtOH (10 ml) was added 10% NaOH aqueous solution (10 mL) at 26° C. The mixture was stirred for 30 min and then concentrated before the addition of water (20 mL) and washing with ethyl acetate (2×20 mL). The aqueous layer was acidified with 2N HCL until pH 3 and extracted with ethyl acetate (2×20 ml). The organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the title compound which was used in next step without further purification.

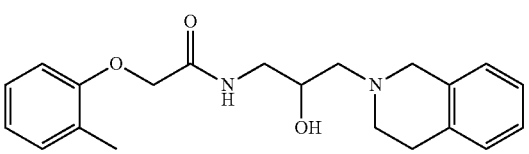
Step 3: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(4-methoxyphenoxy)acetamide



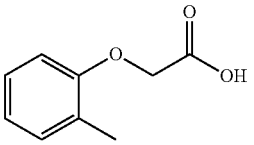
A mixture of compound 2-(4-methoxyphenoxy)acetic acid (100 mg, 0.55 mmol), 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (113.7 mg, 0.55 mmol), BOP-Cl (177.2 mg, 0.696 mmol) and DIPEA (1 mL) in DCM (10 mL) was stirred at room temperature for 4 h. The solvent was removed by concentration and the crude product was purified by pre-HPLC to give the title compound (13.3 mg, yield 6.5%). ^1H NMR (500 MHz, MeOD): δ 7.11-7.06 (m, 3H), 7.02-7.00 (m, 1H), 6.90-6.60 (m, 4H), 4.45 (s, 2H), 4.01-3.98 (m, 1H), 3.73 (s, 3H), 3.66 (s, 1H), 3.41-3.39 (m, 2H), 2.90-2.87 (m, 2H), 2.81-2.76 (m, 2H), 2.55 (d, J=6.0 Hz, 2H) ppm; ESI-MS (m/z): 371.2 $[M+1]^+$.

Compound 15

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(o-tolyloxy)acetamide

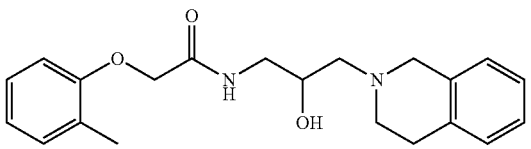


Step 1: 2-(o-tolyloxy)acetic acid



To a stirred solution of o-cresol (200 mg, 1.85 mmol) in MeCN (5 mL) was added ethyl bromoacetate (461 mg, 2.78 mmol) and K_2CO_3 (766 mg, 5.55 mmol). The mixture was stirred at 80° C. for 4 hours. The mixture was filtered and the filtrate concentrated. NaOH (150 mg, 3.70 mmol) and H_2O/EtOH (1:1, 10 mL) was then added to the mixture and the mixture stirred at 50° C. for 4 hours. After cooling, the mixture was acidified by adding 1M HCl then extracted with ethyl acetate (2×30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was used directly in the next step without further purification.

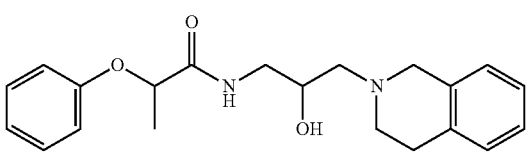
Step 2: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(o-tolyloxy)acetamide



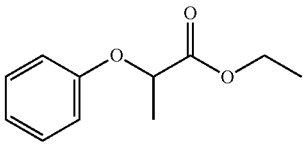
To a stirred mixture of 2-(o-tolyloxy)acetic acid (100 mg, 0.60 mmol) in DCM (5 mL) was added DIEA (116 mg, 0.90 mmol), 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (124 mg, 0.60 mmol) and Bop-Cl (183 mg, 0.72 mmol). The mixture was stirred at 25° C. for 16 hours then quenched by addition of water (20 mL). The resulting mixture was extracted with DCM (3×20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to afford the product (79 mg, Yield 37%). ^1H NMR (400 MHz, MeOD) δ 7.14-7.01 (m, 6H), 6.95-6.82 (m, 2H), 4.55 (s, 2H), 4.04-4.01 (m, 1H), 3.72-3.63 (m, 2H), 3.55-3.46 (m, 1H), 3.42-3.34 (m, 1H), 2.93-2.84 (m, 2H), 2.83-2.74 (m, 2H), 2.57 (d, J=6.3 Hz, 2H), 2.27 (s, 3H). LCMS (m/z): 355.1 (M+1).

Compound 19

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-phenoxypropanamide

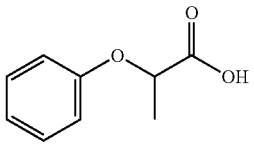


Step 1: ethyl 2-phenoxypropanoate



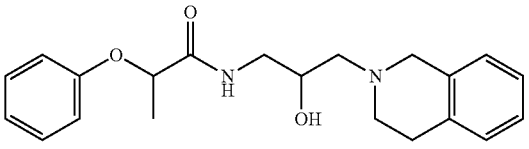
To a solution of NaH (765 mg, 31.89 mmol) in DMF (10 mL) was added phenol (1 g, 10.63 mmol) at 25° C. The mixture was heated at reflux temperature for 15 min, and then ethyl 2-bromopropanoate (2.3 g, 12.75 mmol) was added. The resulting mixture was stirred at 25° C. for another 16 h before quenching with water (50 mL). The mixture was extracted with ethyll acetate (3×20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the title compound (1.8 g, 85.7%) as colorless oil which was used in next step without further purification.

Step 2: 2-phenoxypropanoic acid



To a solution of ethyl 2-phenoxypropanoate (1.8 g, 0.9 mmol) in EtOH (16 ml) was added a solution of NaOH (0.44 g, 1.1 mmol) in H_2O (4 ml) at 25° C. The mixture was stirred for 30 min before being concentrated. The residue had water (20 mL) added and washed with ethyl acetate (2×20 mL). The aqueous layer was acidified with 2N HCL until pH 3 and extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the title compound (1.1 g, 73.3%) as a white solid which was used in next step without further purification.

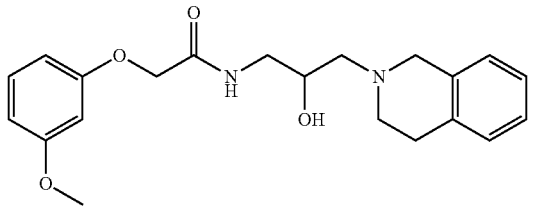
Step 3: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-phenoxypropanamide



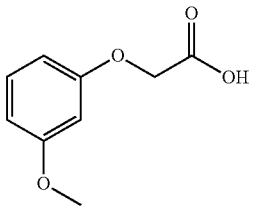
To a solution of 2-phenoxypropanoic acid (200 mg, 1.2 mmol) in DMF (4 ml) was added TEA 364 mg, 3.6 mmol), HOBt (243 mg, 1.8 mmol), EDCI (346 mg, 1.8 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (297 mg, 1.44 mmol) at 24° C. The reaction mixture was stirred for 16 h until TLC showed completion of the reaction. After evaporation of the solvent, the residue was purified by prep-HPLC separation to give the title compound as the formate salt (34 mg, 8%). ^1H NMR (500 MHz, MeOD): δ 8.40 (s, 1H), 7.34-7.25 (m, 5H), 7.17 (d, J=7.2 Hz, 1H), 7.00-6.96 (m, 3H), 4.78-4.76 (m, 1H), 4.26-4.11 (m, 3H), 3.43-3.33 (m, 4H), 3.14-3.12 (m, 2H), 3.08-3.02 (m, 1H), 2.95-2.90 (m, 1H), 1.57 (d, J=6.4 Hz, 3H) ppm; ESI-MS (m/z): 354.2 $[M+1]^+$.

Compound 20

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(3-methoxyphenoxy)acetamide

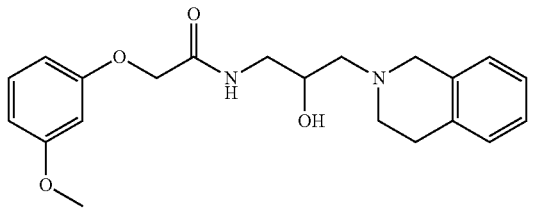


Step 1: 2-(3-methoxyphenoxy)acetic acid



To a stirred mixture of 3-methoxyphenol (200 mg, 1.61 mmol) in MeCN (5 mL) was added ethyl bromoacetate (402 mg, 2.42 mmol) and K_2CO_3 (672 mg, 4.83 mmol). The mixture was stirred at 80° C. for 4 hours, filtered and the filtrate concentrated. NaOH (129 mg, 3.22 mmol) and H2O/EtOH (1:1, 10 mL) was added to the mixture. The reaction mixture was stirred at 50° C. for 4 hours then acidified by 1M HCl and then extracted with ethyl acetate (2×30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated with the residue used directly for the next step. LCMS (m/z): 183.0 (M+1).

Step 2: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(3-methoxyphenoxy)acetamide

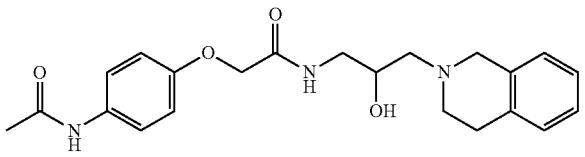


To a stirred mixture of 2-(3-methoxyphenoxy)acetic acid (100 mg, 0.549 mmol) in DCM (5 mL) was added DIEA (106 mg, 0.824 mmol), 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (113 mg, 0.549 mmol) and Bop-Cl (168 mg, 0.66 mmol). The mixture was stirred at 25° C. for 16

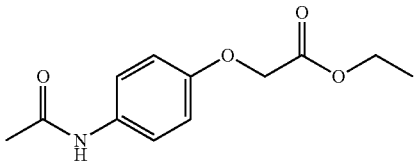
hours then the reaction mixture was quenched with water (20 mL), extracted with DCM (3×20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to afford the desired product (61 mg, Yield 32%). ^1H NMR (400 MHz, MeOD) δ 7.21 (dd, $J_1=J_2=8.0$ Hz, 1H), 7.17-7.03 (m, 4H), 6.59-6.51 (m, 3H), 4.52 (s, 2H), 4.05-4.01 (m, 1H), 3.77 (s, 3H), 3.73 (d, J=2.8 Hz, 2H), 3.47-3.37 (m, 2H), 2.92 (d, J=5.2 Hz, 2H), 2.87 (d, J=5.2 Hz, 2H), 2.61 (d, J=6.0 Hz, 2H). LCMS (m/z): 371.1 (M+1).

Compound 21

2-(4-acetamidophenoxy)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)acetamide

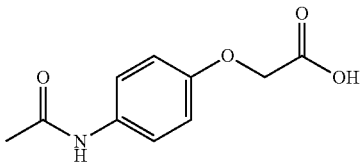


Step 1: ethyl 2-(4-acetamidophenoxy)acetate



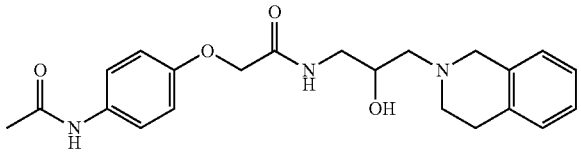
To a solution of N-(4-hydroxyphenyl)acetamide (500 mg, 3.31 mmol) in CH_3CN (10 mL) was added ethyl 2-bromo-2-methylpropanoate (663 mg, 3.97 mmol) and K_2CO_3 (3 g, 21.7 mmol) at 25° C. The mixture was heated at reflux for 16 h. The mixture had water (100 mL) added and extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the title compound which was used in next step without further purification.

Step 2: 2-(4-acetamidophenoxy)acetic acid



To a solution of ethyl 2-(4-acetamidophenoxy)acetate (237 mg, 1 mmol) in EtOH (10 ml) was added 10% NaOH aqueous solution (10 mL) at 26° C. The mixture was stirred for 30 min and then concentrated. The residue was diluted with water (20 mL) and washed ethyl acetate (2×20 mL). The aqueous layer was then acidified with 2N HCL until pH 3 and extracted with ethyl acetate (2×20 ml). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the title compound which was used in next step without further purification.

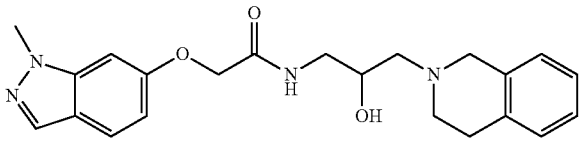
Step 3: 2-(4-acetamidophenoxy)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)acetamide



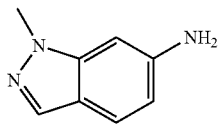
A mixture of compound 2-(4-methoxyphenoxy)acetic acid (100 mg, 0.51 mmol), 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (132 mg, 0.51 mmol), BOP-Cl (156 mg, 0.61 mmol) and DIPEA (1 mL) in DCM (10 mL) was stirred at room temperature for 4 h. The solvent was removed by concentration and the crude product was purified by pre-HPLC to give the title compound (7.8 mg, yield: 3.8%). ^1H NMR (500 MHz, MeOD): δ 7.45 (d, d, J=8.8 Hz, 2H), 7.11-7.05 (m, 3H), 7.02-7.00 (m, 1H), 6.88 (d, J=8.8 Hz, 2H), 4.50 (s, 2H), 4.01-3.98 (m, 1H), 3.66 (d, J=3.2 Hz, 2H), 3.41 (dd, J=0.8, 6.0 Hz, 2H), 2.89-2.87 (m, 2H), 2.80-2.76 (m, 2H), 2.55 (d, J=6.0 Hz, 2H), 2.08 (s, 3H) ppm; ESI-MS (m/z): 398.2 $[M+1]^+$.

Compound 23

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((1-methyl-1H-indazol-6-yl)oxy)acetamide



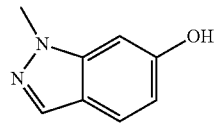
Step 1: 1-methyl-1H-indazol-6-amine



To a solution of 1-methyl-6-nitro-1H-indazole (1.2 g, 0.7 mmol) in EtOH (50 ml) and THF (15 ml) was added PtO_2 (125 mg) at 26° C. The mixture was stirred for 1.5 h at 26° C. under a H_2 atmosphere at 30 Psi. Once the reaction was complete by TLC analysis, the mixture was filtered and the filtrate concentrated to give the target crude product as a white

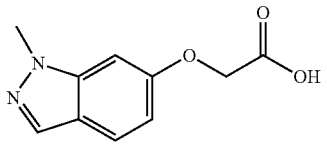
solid which was used in the next step without further purification (1.0 g, Yield 90%). LCMS (m/z): 148.1 (M+1).

Step 2: 1-methyl-1H-indazol-6-ol



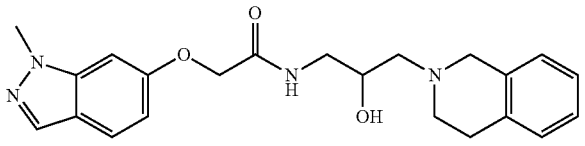
To a solution of 1-methyl-1H-indazol-6-amine (300 mg, 2.04 mmol) in H_2O/H_2SO_4=1:1 (5 ml) was added $NaNO_2$ (141 mg, 2.04 mmol) at 0° C. The mixture was then stirred for 2 h at 25° C. before being added to water (0.5 ml) and stirred for a further 2 h at 120° C. Once the reaction was complete by TLC, the mixture was treated with $NaHCO_3$ until pH=7. The mixture was then extracted with ethyl acetate (2×10 ml) and the organic layer washed with brine (20 ml), dried over Na_2SO_4 and concentrated to give 1-methyl-1H-indazol-6-ol as a red solid which was used in the next step without further purification (300 mg, 99.0%). LCMS (m/z):149.1 (M+1).

Step 3: 2-((1-methyl-1H-indazol-6-yl)oxy)acetic acid



To a solution of NaH (146 mg, 6.06 mmol) in DMF (3 mL) was added 1-methyl-1H-indazol-6-ol (300 mg, 2.02 mmol) at 25° C. After stirring for 5 minutes, ethyl 2-bromoacetate (406 mg, 2.43 mmol) was added and stirred for 16 h at 25° C. The mixture was then diluted with water (50 mL) and washed with ethyl acetate (2×20 mL). The water layer was then acidified by adding with 2N HCL until pH3 and then extracted with ethylacetate (2×20 ml). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the crude product (300 mg, 63.4%) as colorless oil. It was used in next step without further purification. LCMS (m/z): 207.1 (M+1).

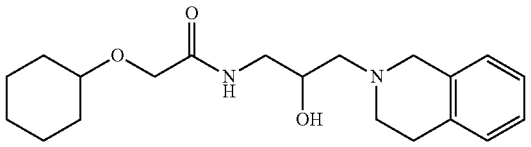
Step 4: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((1-methyl-1H-indazol-6-yl)oxy) acetamide



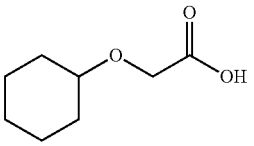
To a solution of 2-((1-methyl-1H-indazol-6-yl)oxy)acetic acid (200 mg, 0.97 mmol) in DMF (4 ml) was added TEA (294 mg, 2.91 mmol), HOBt (196 mg, 1.45 mmol), EDCI (278 mg, 1.45 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (240 mg, 1.2 mmol) at 27° C. The reaction mixture was stirred for 16 h at 27° C. Once the reaction was complete and evaporation of the solvent, the mixture was purified by preparative HPLC to give the formate salt of the title compound (26 mg, 11.9%) as a white solid. ^1H NMR (400 MHz, MeOD) δ 7.91 (s, 1H), 7.67 (d, J=8.8 Hz, 1H), 7.27-7.13 (m, 4H), 7.02 (s, 1H), 6.95 (dd, J_1=8.8 Hz, J_2=2.0 Hz, 1H), 4.68 (s, 2H), 4.26-4.25 (m, 3H), 4.02 (s, 3H), 3.47-3.33 (m, 4H), 3.14-3.06 (m, 4H). LCMS (m/z): 395.2 (M+1).

Compound 24

2-(cyclohexyloxy)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)acetamide

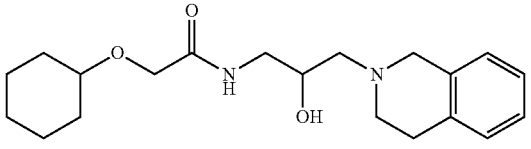


Step 1: 2-(cyclohexyloxy)acetic acid



To a solution of compound NaH (719 mg, 29.94 mmol) in DMF (10 mL) was added cyclohexanol (1 g, 9.98 mmol) at 0° C. After stirring for 5 minutes, ethyl 2-bromoacetate (2 g, 11.98 mmol) was added and the mixture stirred for another 16 h. Once complete, the mixture was treated with water (50 mL) and washed with ethyl acetate (2×20 mL). The water layer was treat with 2N HCL until pH 3. The water layer was extracted with ethyl acetate (2×20 ml) and the combined organic layers washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the desired product (500 mg, 27.8%) as colorless oil which was used in next step without further purification.

Step 2: 2-(cyclohexyloxy)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)acetamide

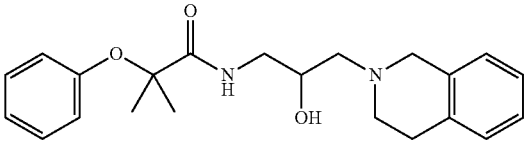


To a solution of 2-(cyclohexyloxy)acetic acid (100 mg, 0.632 mmol) in DMF (3 ml) was added TEA (191 mg, 1.896

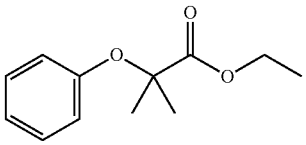
mmol), HOBT (128 mg, 0.948 mmol), EDCI (182 mg, 0.948 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl) propan-2-ol (156 mg, 0.758 mmol) at 27° C. The mixture was stirred for 16 h until the reaction was complete. After evaporation of the solvent, the residue was purified by prep-HPLC to afford the title compound as the formate salt (26 mg, Yield 11.9%). ^{1}H NMR (400 MHz, MeOD): δ 8.48 (s, 1H), 7.27-7.22 (m, 3H), 7.16-7.15 (m, 1H), 4.23-4.18 (m, 3H), 4.00 (s, 2H), 3.44-3.33 (m, 3H), 3.13-3.02 (m, 4H), 1.95-1.13 (m, 2H), 1.78-1.76 (m, 2H), 1.63-1.61 (m, 1H), 1.37-1.27 (m, 5H) ppm; ESI-MS (m/z): 469.3 $[M+1]^+$.

Compound 25

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-methyl-2-phenoxypropanamide

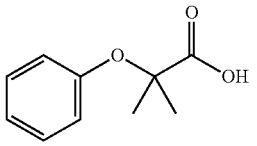


Step 1: ethyl 2-methyl-2-phenoxypropanoate



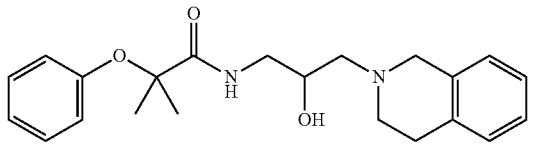
To a solution of phenol (2 g, 21.25 mmol) in CH_3CN (50 mL) was added ethyl 2-bromo-2-methylpropanoate (5 g, 25.5 mmol) and Cs_2CO_3 (20 g, 63.75 mmol) at 25° C. The mixture was heated at reflux for 16 h then water (100 mL) added and extracted with ethyl acetate (2×50 mL). The organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the title compound (2.1 g, 47.7%) as colorless oil which was used in next step without further purification.

Step 2: 2-methyl-2-phenoxypropanoic acid



To a solution of ethyl 2-methyl-2-phenoxypropanoate (2.0 g, 9.6 mmol) in EtOH (16 ml) was added a solution of NaOH (0.46 g, 11.5 mmol) in H_2O (4 ml) at 26° C. The mixture was stirred for 30 min then concentrated. Water was added (20 mL) and washed with ethyl acetate (2×20 mL). The aqueous layer was acidified with 2N HCL until pH 3 and extracted with ethyl acetate (2×20 ml). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the title compound (1.6 g, 94.1%) as a white solid which was used in next step without further purification.

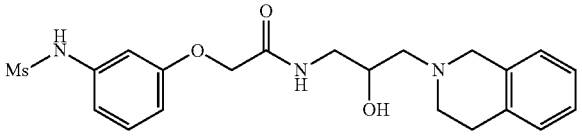
Step 3: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-methyl-2-phenoxypropanamide



To a solution of compound 2-methyl-2-phenoxypropanoic acid (200 mg, 1.11 mmol) in DMF (4 ml) was added TEA (336 mg, 3.33 mmol), HOBt (225 mg, 1.66 mmol), EDCI (320 mg, 1.66 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (320 mg, 1.33 mmol) at 24° C. The reaction mixture was stirred for 16 h at 24° C. After evaporation of the solvent, the residue was purified by prep-HPLC separation to give the title compound as the formate salt (33 mg, 8%). ^{1}H NMR (500 MHz, MeOD): δ 8.40 (s, 1H), 7.32-7.25 (m, 5H), 7.19 (d, J=6.8 Hz, 1H), 7.09 (t, J=7.6 Hz, 1H), 6.98-6.96 (m, 2H), 4.33 (s, 2H), 4.29-4.22 (m, 1H), 3.49 (t, J=6.4 Hz, 2H), 3.42 (d, J=5.6 Hz, 2H), 3.16-3.07 (m, 4H), 1.51 (s, 6H) ppm; ESI-MS (m/z): 369.5 $[M+1]^+$.

Compound 28

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(3-(methylsulfonamido)phenoxy)acetamide

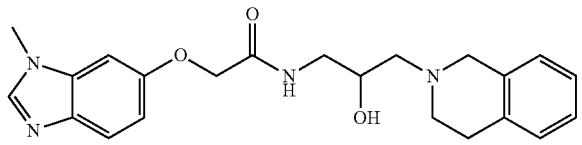


MsCl (23 mg, 0.2 mmol) was added to a cooled 0° C. stirred solution of 2-(3-aminophenoxy)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)acetamide (71 mg, 0.2 mmol) in Et_3N (0.1 mL) and DCM (10 mL). After stirred for 2 h, the solvent was removed by concentration. The residue was purified by prep-HPLC to afford the title compound. ^{1}H NMR (400 MHz, MeOD): δ 7.26-7.22 (m, 1H), 7.11-7.01 (m, 4H), 6.91-6.85 (m, 2H), 6.71-6.68 (m, 1H), 4.53 (s, 2H), 4.03-4.00 (m, 1H), 3.69 (s, 2H), 3.43-3.88 (m, 1H), 3.13-3.12

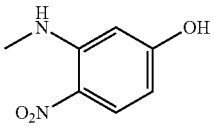
(m, 1H), 2.96 (s, 3H), 2.89 (d, J=6 Hz, 1H), 2.82 (d, J=5.6 Hz, 1H), 2.57 (t, J=6 Hz, 1H) ppm; ESI-MS (m/z): 434.1 $[M+1]^+$.

Compound 30

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((1-methyl-1H-benzo[d]imidazol-6-yl)oxy)acetamide

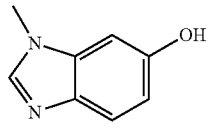


Step 1: 3-(methylamino)-4-nitrophenol



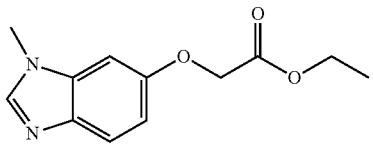
The solution of 3-fluoro-4-nitrophenol (1 g, 6.37 mmol) in aqueous $MeNH_2$ solution (5 mL) was stirred at 85° C. for 5 h. After cooling to room temperature, the solution was diluted with water (30 mL) and concentrated HCl added to adjust to pH 1. The resulting precipitate was collected by filtration and the solid dried under vacuum to give the crude product which was used without further purification (1.1 g, 95% yield). LCMS (m/z): 169.1 (M+1).

Step 2: 1-methyl-1H-benzo[d]imidazol-6-ol



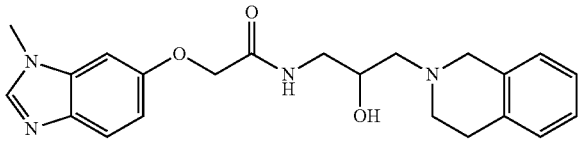
Fe Powder (4.33 g, 77.4 mmol) was added to a solution of 3-(methylamino)-4-nitrophenol (1.3 g, 7.74 mmol) in HCOOH (30 mL) and the mixture heated to 100° C. for 16 h. After cooling to room temperature, MeOH (250 mL) was added to mixture and filtered over a pad of Celite. The filtrate was collected, concentrated and the residue purified by column chromatography to give the crude desired product (1.2 g) and was used directly in the next step. LCMS (m/z): 149.06 (M+1).

Step 3: ethyl 2-((1-methyl-1H-benzo[d]imidazol-6-yl)oxy)acetate



The mixture of 1-methyl-1H-benzo[d]imidazol-6-ol (600 mg, 4.03 mmol), $BrCH_2COOEt$ (372 mg, 4.03 mmol) and K_2CO_3 (1.1 g, 8.06 mmol) in DMF (8 mL) was stirred at room temperature for 16 h. DCM (100 mL) and water (100 mL) was then added to the reaction and the organic layer washed with water (50 mL), brine (50 mL) and dried over Na_2SO_4 before filtering and concentration to give the crude desired product (560 mg, Yield 60%). LCMS (m/z): 235.1 (M+1).

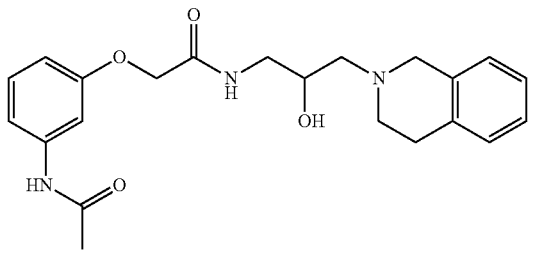
Step 4: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((1-methyl-1H-benzo[d]imidazol-6-yl)oxy)acetamide



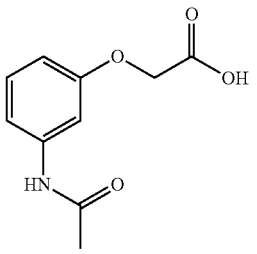
A neat solution of ethyl 2-((1-methyl-1H-benzo[d]imidazol-6-yl)oxy)acetate (100 mg, 0.427 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (88 mg, 0.427 mmol) was stirred at room temperature for 2 days until TLC showed the completion of the reaction. The solution concentrated and the residue purified by prep-HPLC to give desired product as the TFA salt (19.1 mg, Yield 11.3%). ^1H NMR (400 MHz, MeOD). δ 9.21 (s, 1H), 7.80 (d, J=8.8 Hz, 1H), 7.49 (s, 1H), 7.40-7.20 (m, 5H), 4.74 (s, 2H), 4.53 (br.s, 2H), 4.37-4.32 (m, 1H), 4.11 (s, 3H), 3.68 (br.s, 2H), 3.53-3.12 (m, 6H). LCMS (m/z): 395.1 (M+1).

Compound 31

2-(3-acetamidophenoxy)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)acetamide

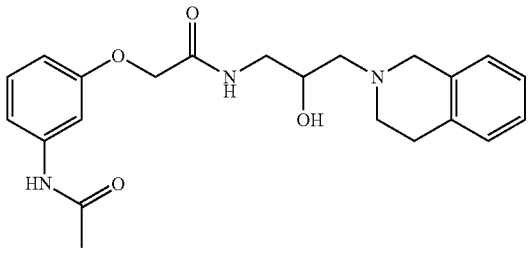


Step 1: 2-(3-acetamidophenoxy) acetic acid



To a stirred mixture of N-(3-hydroxyphenyl)acetamide (300 mg, 2.0 mmol) in MeCN (5 mL) was added ethyl bromoacetate (500 mg, 3 mmol) and K_2CO_3 (828 mg, 6 mmol). The mixture was stirred at 80° C. for 4 hours, filtered and the filtrate was concentrated. NaOH (80 mg, 2 mmol) and water: EtOH (1:1, 10 mL) was added to the mixture. This mixture was then stirred at 50° C. for 4 hours before being acidified by 1M HCl, extracted with ethyl acetate (2×30 mL). The combined extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated with the residue used directly for the next step. LCMS (m/z): 183.0 (M+1).

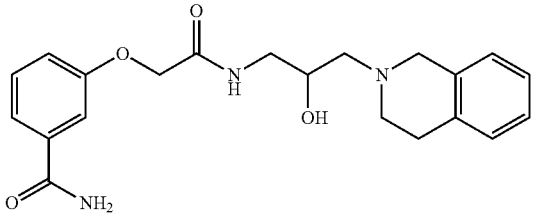
Step 2: 2-(3-acetamidophenoxy)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)acetamide



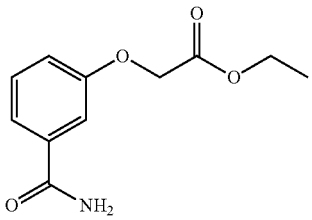
To a stirred mixture of 2-(3-acetamidophenoxy) acetic acid (85 mg, 0.41 mmol) in DCM (5 mL) was added TEA (0.5 mL), 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (83.8 mg, 0.41 mmol) and HATU (171 mg, 0.451 mmol). The mixture was stirred at 25° C. for 3 hours. The reaction mixture was quenched by addition of water (20 mL) and extracted with DCM (3×20 mL) and the combined extracts washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to afford the title product (55 mg, Yield 35%). ^{1}H NMR (400 MHz, MeOD) δ=7.36 (s, 1H), 7.27-7.17 (m, 1H), 7.19-7.01 (m, 6H), 6.68-6.66 (m, 1H), 4.53 (s, 2H), 4.03-4.00 (m, 1H), 3.71-3.62 (m, 2H), 3.50-3.35 (m, 2H), 2.95-2.85 (m, 2H), 2.83-2.74 (m, 2H), 2.56 (d, J=6.3 Hz, 2H), 2.12 (s, 3H). LCMS (m/z): 398.1 (M+1).

Compound 34

3-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)amino)-2-oxoethoxy)benzamide

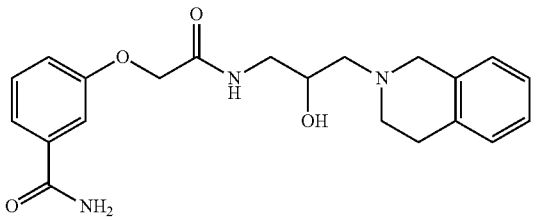


Step 1: ethyl 2-(3-carbamoylphenoxy)acetate



To a stirred mixture of 3-hydroxybenzamide (300 mg, 2.19 mmol) in MeCN (5 mL) was added ethyl bromoacetate (545 mg, 3.29 mmol) and K_2CO_3 (907 mg, 6.57 mmol). The mixture was stirred at 80° C. for 4 hours. The mixture was filtered and the filtrate concentrated. The residue was directly for the next step. LCMS (m/z): 224.1 (M+1).

Step 2: 3-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)amino)-2-oxoethoxy)benzamide

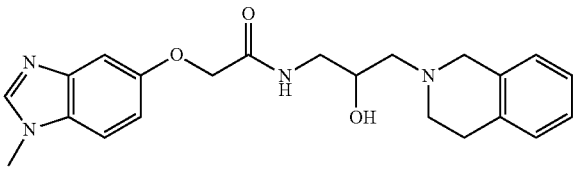


To a stirred mixture of ethyl 2-(3-carbamoylphenoxy)acetate (150 mg, 0.673 mmol) in EtOH (1 mL) was added 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (138.6 mg, 0.673 mmol). The mixture was stirred at 120° C. for 0.5 hour under mediated heating. After evaporation of the solvent, the residue was purified by prep-HPLC to afford the desired title product (64 mg, Yield 25%). ^{1}H NMR (400 MHz, MeOD) δ 7.53 (d, J=8.0 Hz, 1H), 7.48 (s, 1H), 7.39 (dd, J_1=J_2=7.9 Hz, 1H), 7.12-7.00 (m, 5H), 4.60 (s, 2H), 4.04-4.01

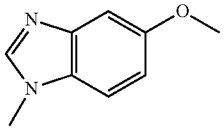
(m, 1H), 3.74-3.65 (m, 2H), 3.47-3.39 (m, 2H), 2.95-2.87 (m, 2H), 2.85-2.77 (m, 2H), 2.58 (d, J=6.0 Hz, 2H). LCMS (m/z): 384.1 (M+1).

Compound 46

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)acetamide

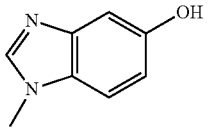


Step 1: 5-methoxy-1-methyl-1H-benzo[d]imidazole



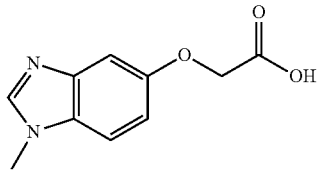
To a solution of NaH (972 mg, 40.5 mmol) in DMF (20 mL) was added 5-methoxy-1H-benzo[d]imidazole (2.0 g, 13.5 mmol) at 27° C. After stirring for 5 minutes, MeI (2.3 g, 16.2 mmol) was added and the resulting mixture was stirred for 16 h. The mixture was then diluted with water (100 mL) and extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the crude product (1.2 g, 54.5%) as a grown solid. This crude was used in next step without further purification. LCMS (m/z): 163.1 (M+1).

Step 2: 1-methyl-1H-benzo[d]imidazol-5-ol



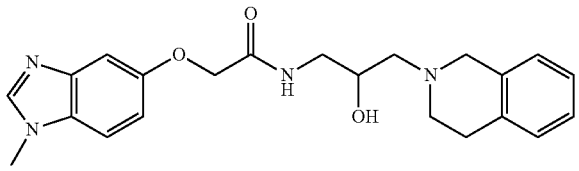
To a solution of 5-methoxy-1-methyl-1H-benzo[d]imidazole (500 mg, 3.08 mmol) in CH_2Cl_2 (6 ml) was added BBr_3 (3.1 g, 12.33 mmol) dropwise at 0° C. After addition, the mixture was stirred for 2 h at 0° C. The mixture was then quenched by slow addition to ice water (50 mL). The resulting mixture was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the title compound (100 mg, 21.9%) as a white solid which was used in next step without further purification. LCMS (m/z): 149.1 (M+1).

Step 3: 2-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)acetic acid



To a solution of NaH (204 mg, 8.49 mmol) in DMF (5 mL) was added 1-methyl-1H-benzo[d]imidazol-5-ol (420 mg, 2.83 mmol) at 28° C. After being stirred for 5 minutes, ethyl 2-bromoacetate (568 mg, 3.4 mmol) was added and the resulting mixture stirred for a further 16 h under the reaction was complete by TLC. The mixture was treated with water (50 mL) and extracted with ethyl acetate (2×20 mL). The water layer was treated with 2N HCl until pH 3 and extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the product (160 mg, 24.1%) as white solid which was used in next step without further purification. LCMS (m/z): 207.1 (M+1).

Step 4: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)acetamide

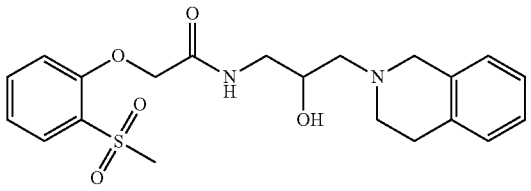


To a solution of 2-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)acetic acid (160 mg, 0.776 mmol) in DMF (4 ml) was added TEA (336 mg, 3.33 mmol), HOBt (157 mg, 1.164 mmol), EDCI (223 mg, 1.164 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (192 mg, 0.931 mmol) at 29° C. The reaction mixture was stirred for 16 h at 29° C. until TLC showed the reaction to be complete. After evaporation of the solvent, the mixture was purified by preparative HPLC to give the title compound (13.1 mg, 4.2%) as colorless oil. ^1H NMR (400 MHz, MeOD) δ 8.05 (s, 1H), 7.45 (d, J=8.8 Hz, 1H), 7.21 (d, J=2.0 Hz, 1H), 7.09-6.97 (m, 5H), 4.59 (s, 2H), 4.03-3.97 (m, 1H), 3.84 (s, 3H), 3.65 (dd,

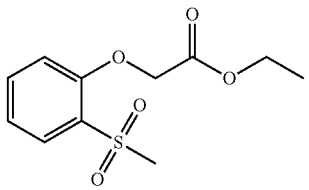
J1=14.8 Hz, J2=30.4 Hz, 2H), 3.47-3.42 (m, 2H), 2.88 (t, J=5.6 Hz, 2H), 2.72 (t, J=5.6 Hz, 2H), 2.53-2.51 (m, 2H). LCMS (m/z): 395.2 (M+1).

Compound 37

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(2-(methylsulfonyl)phenoxy)acetamide

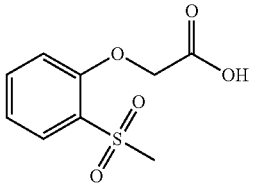


Step 1: ethyl 2-(2-(methylsulfonyl)phenoxy)acetate



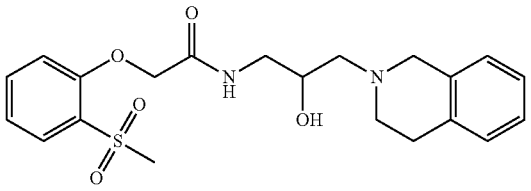
To a solution of 2-(methylsulfonyl)phenol (200 mg, 1.16 mmol) in CH_3CN (10 mL) was added ethyl 2-bromo-2-methylpropanoate (232 mg, 1.39 mmol) and K_2CO_3 (690 mg, 5 mmol) at 25° C. The mixture was refluxed for 16 h and then quenched by addition of water (100 mL). The resulting mixture was extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the title compound which was used in next step without further purification.

Step 2: 2-(2-(methylsulfonyl)phenoxy)acetic acid



To a solution of ethyl 2-(2-(methylsulfonyl)phenoxy)acetate (750 mg, 2.9 mmol) in EtOH (15 ml) was added 10% NaOH aqueous solution (15 mL) at 26° C. The mixture was stirred for 30 min and then concentrated and the residue diluted with water (20 mL) and washed with ethyl acetate (2×20 mL). The aqueous layer was then acidified with 2N HCL until pH 3 and then extracted with ethyl acetate (2×20 ml). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the title compound which was used in next step without further purification.

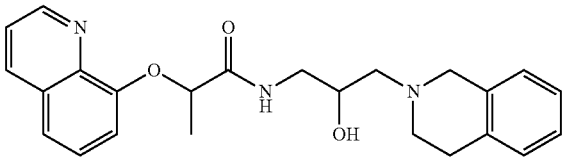
Step 3: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(2-(methylsulfonyl)phenoxy)acetamide



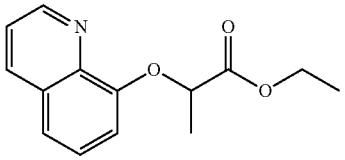
A mixture of compound 2-(4-methoxyphenoxyl)acetic acid (100 mg, 0.43 mmol), 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (89 mg, 0.43 mmol), BOP-Cl (171 mg, 0.67 mmol) and DIPEA (1 mL) in DCM (10 mL) was stirred at room temperature for 4 h. The solvent was removed by concentration and the crude product was purified by pre-HPLC to give the title compound (12 mg, 6.7%). ^1H NMR (500 MHz, MeOD): δ 7.96 (dd, J=1.6, 8.0 Hz, 1H), 7.75 (t, J=7.2 Hz, 1H), 7.29-7.24 (m, 2H), 7.13-7.02 (m, 4H), 4.82 (s, 2H), 4.06-4.03 (m, 1H), 3.72 (d, J=2.4 Hz, 2H), 3.53 (dd, J=7.2, 13.2 Hz, 1H), 3.37-3.33 (m, 1H), 3.29 (s, 3H), 2.93-2.90 (m, 2H), 2.86-2.83 (m, 2H), 2.62-2.6 (m, 2H) ppm; ESI-MS (m/z): 419.1 $[M+1]^+$.

Compound 39

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(quinolin-8-yloxy)propanamide



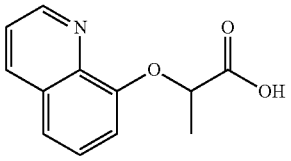
Step 1: ethyl 2-(quinolin-8-yloxy)propanoate



To a solution of compound NaH (100 mg, 4.14 mmol) in DMF (3 mL) was added quinolin-8-ol (200 mg, 1.38 mmol) at 26° C. After stirred for 5 minutes, ethyl 2-bromopropanoate

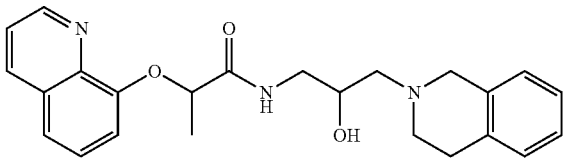
(300 mg, 1.65 mmol) was added and the reaction mixture stirred for 16 h at 26° C. The mixture was then diluted with water (20 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give ethyl 2-(quinolin-8-yloxy)propanoate (200 mg, 59.2%) as colorless oil which was used in next step without further purification. (304 mg, Yield 90%).

Step 2: 2-(quinolin-8-yloxy)propanoic acid



To a solution of ethyl 2-(quinolin-8-yloxy)propanoate (100 mg, 0.4 mmol) in EtOH (1 ml) was added a solution of NaOH (24 mg, 0.6 mmol) in H_2O (0.5 ml) at 27° C. The mixture was stirred for 30 min at 27° C. The mixture was then concentrated and the residue treated with water (5 mL) and extracted with ethyl acetate (2×5 mL). The water layer was then treated with 2N HCl until pH 3 before being extracted with ethyl acetate (2×5 ml). The organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the title product (70 mg, 80.5%) as a white solid which was used in next step without further purification.

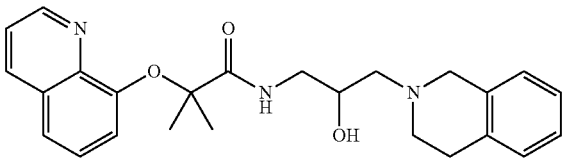
Step 3: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(quinolin-8-yloxy)propanamide



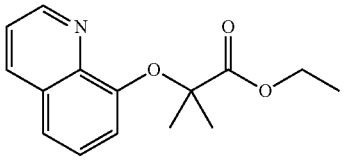
To a solution of 2-(quinolin-8-yloxy)propanoic acid (60 mg, 0.276 mmol) in DMF (4 ml) was added TEA (84 mg, 1.1 mmol), HOBt (60 mg, 0.41 mmol), EDCI (79.8 mg, 0.41 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl) propan-2-ol (72 mg, 0.331 mmol) at 28° C. The reaction mixture was stirred for 16 h until TLC showed the reaction was completed. After evaporation of the solvent, the residue was purified by HPLC separation to give the TFA salt of N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(quinolin-8-yloxy)propanamide (23 mg, 20.5%) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 9.15 (d, J=4.0 Hz, 1H), 9.04-9.00 (m, 1H), 8.06-8.02 (m, 1H), 7.89-7.80 (m, 2H), 7.57 (d, J=7.6 Hz, 1H), 7.33-7.19 (m, 4H), 5.29-5.27 (m, 1H), 4.50 (br.s, 2H), 4.30-4.27 (m, 1H), 3.69 (br.s, 2H), 3.45-3.42 (m, 2H), 3.26-3.20 (m, 4H), 2.76 (d, J=9.6 Hz, 3H). LCMS (m/z): 406.2 (M+1).

Compound 43

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-methyl-2-(quinolin-8-yloxy)propanamide

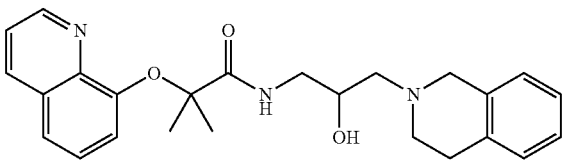


Step 1: ethyl 2-methyl-2-(quinolin-8-yloxy)propanoate



To a solution of compound NaH (248 mg, 10.2 mmol) in DMF (10 mL) was added quinolin-8-ol (500 mg, 3.44 mmol) at 28° C. After stirring for 5 minutes, ethyl 2-bromo-2-methylpropanoate (806 mg, 4.13 mmol) was added and the reaction mixture was stirred for an additional 16 h at 28° C. until the reaction was complete by TLC. The mixture was then diluted with water (50 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the crude product (400 mg, 44.8%) as colorless oil which was used in next step without further purification.

Step 2: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-methyl-2-(quinolin-8-yloxy)propanamide

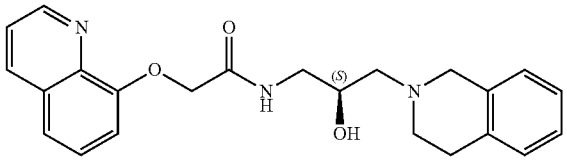


To a solution of ethyl 2-methyl-2-(quinolin-8-yloxy)propanoate (120 mg, 0.46 mmol) in EtOH (0.5 ml) was added 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (0.46 mmol) at 29° C. The mixture was stirred for 1 hour at 120° C. under microwave heating. The solvent was removed and the residue purified by prep-HPLC to afford the title compound (19.5 mg, Yield 10.1%). ^{1}H NMR (400 MHz, MeOD): δ 8.95-8.93 (m, 1H), 8.34 (dd, J=8.4, 1.6 Hz, 1H), 7.69 (d, J=8 Hz, 1H), 7.56-7.52 (m, 2H), 7.39 (d, J=7.6 Hz, 1H), 7.11-7.02 (m, 3H), 6.94 (d, J=6.4 Hz, 1H), 4.13-4.10 (m,

1H), 3.70-3.53 (m, 2H), 3.48-3.43 (m, 2H), 2.91-2.81 (m, 4H), 2.79-2.64 (m, 2H), 1.57 (s, 6H) ppm; ESI-MS (m/z): 420.3 $[M+1]^+$.

Compound 44

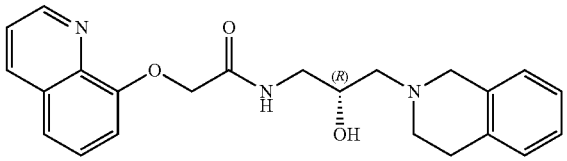
(S)—N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(quinolin-8-yloxy)acetamide



To a stirred mixture of ethyl 2-(quinolin-8-yloxy)acetate (250 mg, 1.08 mmol) in EtOH (2 mL) was added (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (222 mg, 1.08 mmol). The mixture was stirred at 120° C. for 0.5 hour under microwave heating. After evaporation of the solvent, the residue was purified first by prep-TLC and then prep-SFC to afford (140 mg, Yield 36%). ^{1}H NMR (400 MHz, MeOD) 6=8.91 (d, J=4.3 Hz, 1H), 8.42 (d, J=8.3 Hz, 1H), 7.69-7.54 (m, 3H), 7.30 (d, J=7.3 Hz, 1H), 7.12-6.96 (m, 4H), 4.78 (s, 2H), 4.18-4.07 (m, 1H), 3.71 (s, 2H), 3.60-3.49 (m, 1H), 3.48-3.40 (m, 1H), 2.89 (d, J=5.8 Hz, 2H), 2.84 (d, J=4.8 Hz, 2H), 2.69-2.55 (m, 2H). LCMS (m/z): 392.1 (M+1).

Compound 45

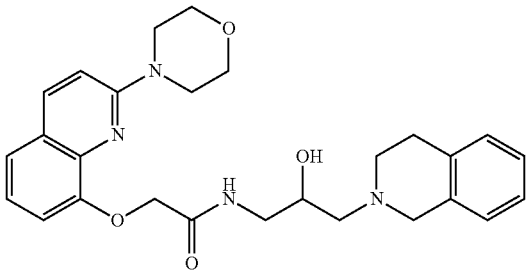
(R)—N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(quinolin-8-yloxy)acetamide



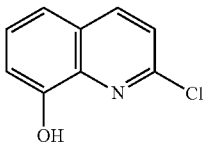
To a stirred mixture of ethyl 2-(quinolin-8-yloxy)acetate (250 mg, 1.08 mmol) in EtOH (2 mL) was added (R)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (222 mg, 1.08 mmol). The mixture was stirred at 120° C. for 0.5 hour under microwave heating. After evaporation of the solvent, the residue was purified first by prep-TLC and then by prep-SFC to afford (160 mg Yield 40%). ^{1}H NMR (400 MHz, MeOD) δ=8.791 (d, J=4.3 Hz, 1H), 8.30 (d, J=8.3 Hz, 1H), 7.51-7.46 (m, 3H), 7.17 (d, J=7.3 Hz, 1H), 6.94-6.85 (m, 4H), 4.65 (s, 2H), 4.00-3.99 (m, 1H), 3.59 (s, 2H), 3.44-3.32 (m, 2H), 2.77-2.71 (m, 4H), 2.53-2.51 (m, 2H). LCMS (m/z): 392.1 (M+1).

Compound 48

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((2-morpholinoquinolin-8-yl)oxy)acetamide

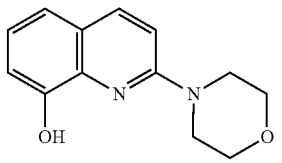


Step 1: 2-chloroquinolin-8-ol



To a stirred mixture of quinoline-2,8-diol (1 g, 6.21 mmol) was added $POCl_3$ (10 mL) and the mixture stirred at 100° C. for 1 hour before cooling. The mixture was then poured into ice-water (100 mL) slowly and filtered. The collected solid was dried and used in next step without further purification. (780 mg, Yield 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J=8.8 Hz, 1H), 7.57 (d, J=8.8 Hz, 1H), 7.48-7.43 (m, 2H), 7.17 (dd, J_1=8.8 Hz, J_1=1.6 Hz, 1H).

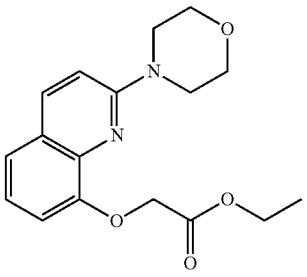
Step 2: 2-morpholinoquinolin-8-ol



To a stirred mixture of 2-chloroquinolin-8-ol (1.7 g crude, 9.5 mmol) was added morpholine (5 mL). The mixture was heated at reflux for 16 hours. After cooling, the mixture was diluted with water (40 mL) and extracted with ethyl acetate

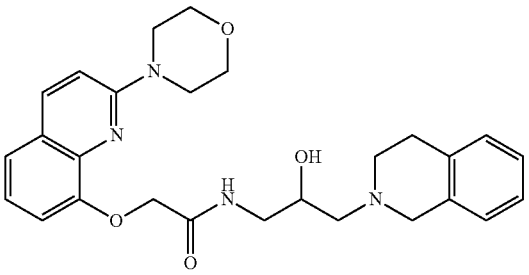
(3×30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was used directly for the next step. (1.6 g, Yield 80%). LCMS (m/z): 231.1 (M+1).

Step 3: ethyl 2-((2-morpholinoquinolin-8-yl)oxy)acetate



To a stirred mixture of 2-morpholinoquinolin-8-ol (200 mg, 0.87 mmol) in MeCN (5 mL) was added ethyl bromoacetate (216 mg, 1.31 mmol) and K_2CO_3 (360 mg, 2.61 mmol). The mixture was stirred at 80° C. for 4 hours. After filtration, the filtrate was concentrated to give crude product which was used directly for the next step (250 mg, Yield 90%).

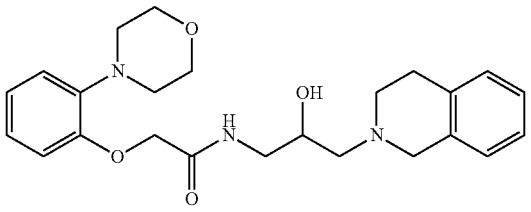
Step 4: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((2-morpholinoquinolin-8-yl)oxy) acetamide



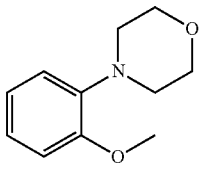
To a stirred mixture of ethyl 2-((2-morpholinoquinolin-8-yl)oxy)acetate (100 mg, 0.316 mmol) in EtOH (2 mL) was added 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl) propan-2-ol (65 mg, 0.316 mmol). The mixture was stirred at 120° C. for 0.5 hour under microwave conditions then after evaporation of solvent, the reaction mixture was purified by prep-HPLC to afford the title product (14 mg, Yield 10%). ^1H NMR (400 MHz, MeOD) δ=8.04 (d, J=9.3 Hz, 1H), 7.43-7.36 (m, 1H), 7.23-7.16 (m, 3H), 7.10-7.00 (m, 3H), 6.97 (d, J=4.8 Hz, 1H), 4.77 (s, 2H), 3.96 (t, J=6.3 Hz, 1H), 3.87-3.83 (m, 4H), 3.77-3.72 (m, 4H), 3.63-3.53 (m, 2H), 3.52-3.45 (m, 1H), 3.40 (d, J=6.3 Hz, 1H), 2.83 (d, J=5.8 Hz, 2H), 2.75-2.67 (m, 2H), 2.56-2.37 (m, 2H). LCMS (m/z): 477.2 (M+1).

Compound 49

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(2-morpholinophenoxy)acetamide

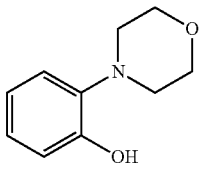


Step 1: 4-(2-methoxyphenyl)morpholine



To a solution of 1-iodo-2-methoxybenzene (1 g, 4.28 mmol) in dioxane (10 mL) was added morpholine (446.8 mg, 5.12 mmol), $Pd_2(dba)_3$ (100 mg, 0.1 mmol), Xantphos (200 mg, 0.3 mmol) and t-BuONa (671 mg, 6.0 mmol). Under a N_2 atmosphere the reaction mixture was heated at reflux temperature for 16 h. The solvent was then removed and the residue dissolved in ethyl acetate and washed with water. The separated organic layer was concentrated to give the crude product which was used in next step without further purification (578 mg Yield 70%). LCMS (m/z): 194.1 (M+1).

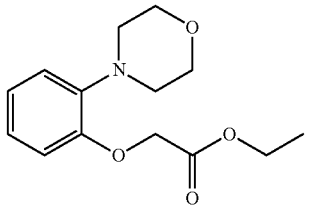
Step 2: 2-morpholinophenol



To a solution of 4-(2-methoxyphenyl)morpholine (200 mg, 1.02 mmol) in CH_2Cl_2 (20 mL) was added BBr_3 (1 mL) at 0° C. The mixture was stirred for 2 h at 0° C. The mixture was then added drop wise to ice-water (50 mL) and the mixture treated with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and

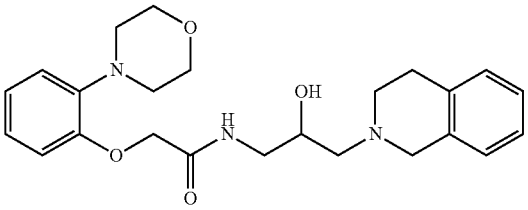
concentrated to give the yellow solid which was used in next step without further purification (165 mg Yield 80%). LCMS (m/z): 180.1 (M+1).

Step 3: ethyl 2-(2-morpholinophenoxy)acetate



A mixture of 2-morpholinophenol (100 mg, 0.56 mmol) and ethyl 2-bromoacetate (200 mg, 0.672 mmol) in CH_3CN (10 mL) was added K_2CO_3 (772.8 mg, 5.6 mmol). The reaction mixture was stirred at 80° C. for 4 h. The solid was removed by filtration and the filtrate concentrated to give a crude material, which was used in the next step without further purification. (130 mg, Yield 90%).

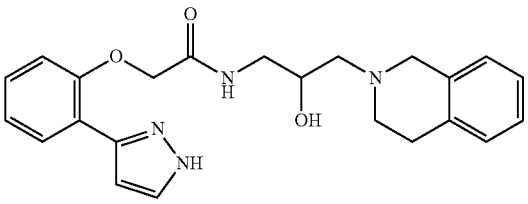
Step 4: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(2-morpholinophenoxy)acetamide



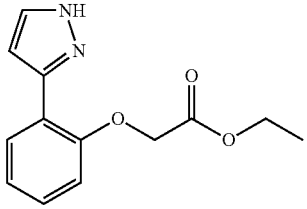
A mixture of ethyl 2-(2-morpholinophenoxy)acetate (53 mg, 0.2 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (41 mg, 0.2 mmol) in EtOH (1 mL) was stirred at 120° C. over microwave for 30 min. The solvent was removed by concentration and the crude product was purified by prep-HPLC separation to afford product the desired title compound (8.0 mg, Yield 10%). ^{1}H NMR (400 MHz, MeOD): 7.09-6.98 (m, 8H), 4.64 (s, 2H), 3.95 (br.s, 1H), 3.89-3.87 (m, 4H), 3.63-3.46 (m, 2H), 3.33-3.30 (m, 1H), 3.07-3.03 (m, 4H), 2.88 (dd, J=6.0 Hz, 2H), 2.77 (dd, J=6.0 Hz, 2H), 2.49 (d, J=6.0 Hz, 2H). LCMS (m/z): 426.2 (M+1).

Compound 50

2-(2-(1H-pyrazol-3-yl)phenoxy)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)acetamide

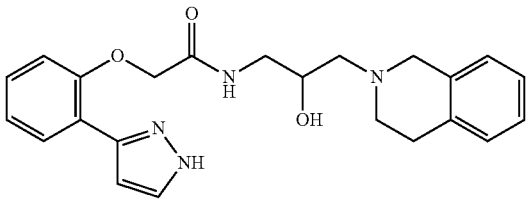


Step 1: ethyl 2-(2-(1H-pyrazol-3-yl)phenoxy)acetate



To a solution of 2-(1H-pyrazol-3-yl)phenol (500 mg, 3.125 mmol), K_2CO_3 (517.5 mg, 3.75 mmol) and ethyl 2-bromoacetate (417.5 mg, 2.5 mmol) in MeCN (20 mL). The mixture was stirred at room temperature for 2 h, at which time TLC showed the completion of the reaction. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give the crude product which was used in next step without further purification.

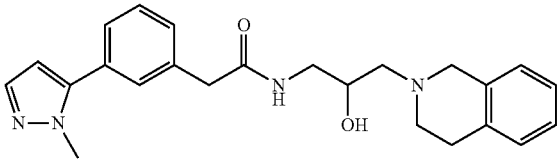
Step 2: 2-(2-(1H-pyrazol-3-yl)phenoxy)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)acetamide



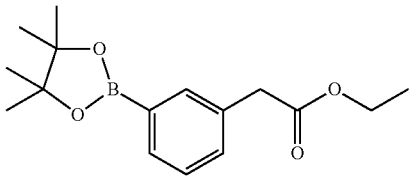
To a solution of ethyl 2-(2-(1H-pyrazol-3-yl)phenoxy)acetate (100 mg, 0.41 mmol) in EtOH (10 mL) was added 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (84 mg, 0.41 mmol). The mixture was stirred at 120° C. under microwave heating for 2 h. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (10 mL), dried over Na_2SO_4 and concentrated to give the crude product. The residue was purified by prep-HPLC to afford the desired title compound (85 mg, 44%). ^{1}H NMR (400 MHz, MeOD): δ 7.71-7.69 (m, 2H), 7.34-7.33 (m, 1H), 7.10-7.01 (m, 6H), 6.74 (d, J=2 Hz, 1H), 4.67 (s, 1H), 4.04-4.02 (m, 1H), 3.67 (s, 2H), 3.50-3.49 (m, 1H), 3.37-3.33 (m, 1H), 2.89-2.87 (m, 2H), 2.81-2.78 (m, 2H), 2.58-2.57 (m, 2H) ppm; ESI-MS (m/z): 469.3 $[M+1]^+$.

Compound 54

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(3-(1-methyl-1H-pyrazol-5-yl)phenyl)acetamide

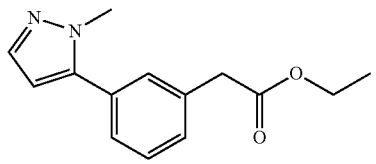


Step 1: ethyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate



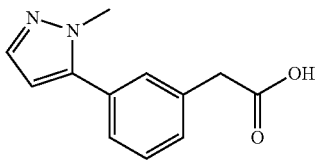
A mixture of ethyl 2-(3-bromophenyl)acetate (1.0 g, 4.1 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.34 g, 5.3 mmol), KOAc (862 mg, 8.8 mmol) and $Pd(pddf)Cl_2$ (50 mg) in dioxane (15 mL) was stirred at 120° C. for 16 h under N_2. The reaction mixture was concentrated and the residue dissolved in water then extracted with EtOAc. The organic layer was concentrated, and the residue purified by column chromatography to give the product which was used directly in the next step.

Step 2: ethyl 2-(3-(1-methyl-1H-pyrazol-5-yl)phenyl)acetate



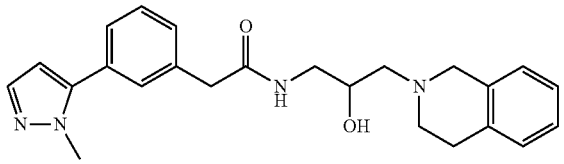
A mixture of ethyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (500 mg, 1.72 mmol), 5-bromo-1-methyl-1H-pyrazole (252 mg, 1.57 mmol), K_2CO_3 (651 mg, 4.71 mmol) and $Pd(dppf)Cl_2$ (20 mg) in a solution of dioxane (10 mL) and H_2O (2.5 mL) was stirred at 120° C. for 30 min under microwave. The catalyst was filtered through a pad of celite and the filtrate concentrated. The residue was purified by column chromatography to give the desired product (270 mg, Yield 70%) and used directly in the next step. LCMS (m/z): 245.1 (M+1).

Step 3: 2-(3-(1-methyl-1H-pyrazol-5-yl)phenyl)acetic acid



To a solution of ethyl 2-(3-(1-methyl-1H-pyrazol-5-yl) phenyl)acetate (300 mg, 1.2 mmol) in MeOH (6 mL) was added aqueous NaOH (1.5 mL, 40 W %). The mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated and the residue dissolved in water and adjusted pH to 5-6 with 2N of HCl. The solution was then extracted with EtOAc and the combined organic layers were concentrated to give the crude product which was used directly in the next step. LCMS (m/z): 231.1 (M+1).

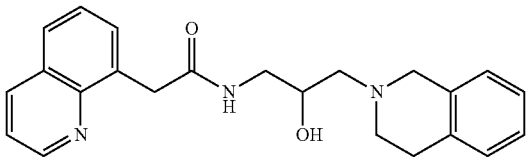
Step 4: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(3-(1-methyl-1H-pyrazol-5-yl) phenyl)acetamide



To a solution of 2-(3-(1-methyl-1H-pyrazol-5-yl)phenyl) acetic acid (150 mg, 0.69 mmol) in DCM (6 mL) was added EDCI (265 mg, 1.38 mmol), HOBt (186 mg, 1.38 mmol), Et_3N (209 mg, 2.07 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (142 mg, 0.69 mmol). The mixture was stirred at room temperature for 16 h then diluted with water (10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were concentrated. The residue was purified by prep-HPLC to give the product as a colorless oil (60 mg, Yield 21%). ^1H NMR (400 MHz, MeOD): 7.47 (s, 1H), 7.43-7.33 (m, 4H), 7.08-7.04 (m, 3H), 6.96-6.94 (m, 1H), 6.35 (s, 1H), 3.96-3.91 (m, 1H), 3.83 (s, 3H), 3.60-3.59 (m, 4H), 3.38-3.20 (m, 2H), 2.84 (t, J=6.0 Hz, 2H), 2.72 (t, J=6.0 Hz, 2H), 2.49 (d, J=6.4 Hz, 2H). LCMS (m/z): 405.2 (M+1).

Compound 60

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(quinolin-8-yl)acetamide

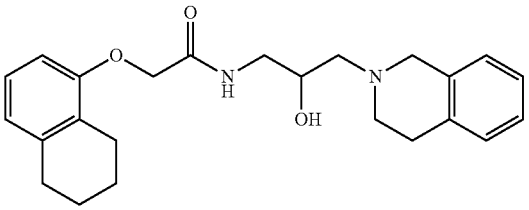


A solution of 2-(quinolin-8-yl)acetic acid (187 mg, 1 mmol), HATU (387.6 mg, 1.02 mmol) and TEA (196.1 mg, 1.94 mmol) in DCM (10 mL) was stirred at room temperature for 10 min. 1-Amino-3-(3,4-dihydroisoquinolin-2(1H)-yl) propan-2-ol (210 mg, 1.0 mmol) was then added, and the solution stirred at for another 3 h, at which point LCMS indicated completion of the reaction. The reaction mixture was diluted with water and extracted with DCM (10 mL×3). The organic layers combined and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by prep-HPLC to give the desired compound (50 mg, Yield 13%). ^1H NMR (400 MHz, MeOD): 8.92 (d, J=2.8 Hz, 1H), 8.33 (d, J=8.0 Hz, 1H), 7.87 (d, J=8.4 Hz, 1H), 7.73 (d, J=6.8 Hz, 1H), 7.55-7.50 (m, 2H), 7.10-6.97 (m, 4H), 4.25 (dd, J_1=10.8 Hz, J_2=14.0 Hz, 2H), 3.90 (m, 1H), 3.54-3.51 (m 2H),

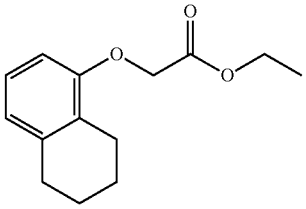
3.32-3.25 (m, 2H), 2.82-2.80 (m, 2H), 2.67-2.66 (m, 2H), 2.40-2.39 (m, 2H). LCMS (m/z): 376.1 (M+1).

Compound 62

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)acetamide

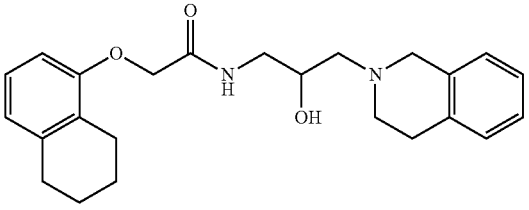


Step 1: ethyl 2-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)acetate



To a stirred mixture of 5,6,7,8-tetrahydronaphthalen-1-ol (200 mg, 1.35 mmol) in MeCN (5 mL) was added ethyl bromoacetate (269 mg, 1.62 mmol) and K_2CO_3 (372 mg, 2.70 mmol). The mixture was stirred at 80° C. for 4 hours. The mixture was filtered, the filtrate concentrated to yield the desired product which used directly for the next step without further purification (300 mg, Yield 95%).

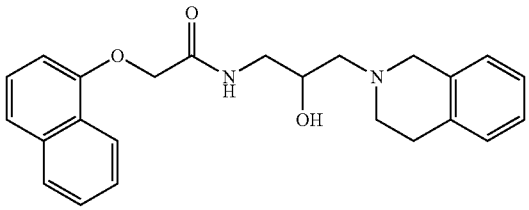
Step 2: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)acetamide



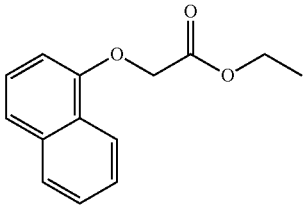
To a stirred mixture of ethyl 2-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)acetate (150 mg, 0.641 mmol) in EtOH (2 mL) was added 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (132 mg, 0.641 mmol). The mixture was stirred at 120° C. for 0.5 hours under microwave heating. After evaporation of the solvent, the residue was purified by prep-HPLC to afford the desired target product N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)acetamide (14 mg, Yield 6%). ^{1}H NMR (400 MHz, MeOD) δ=7.13-7.00 (m, 5H), 6.74 (d, J=7.8 Hz, 1H), 6.65 (d, J=8.3 Hz, 1H), 4.53 (s, 2H), 4.02 (quin, J=5.9 Hz, 1H), 3.72-3.63 (m, 2H), 3.53-3.45 (m, 1H), 3.39 (d, J=6.3 Hz, 1H), 2.96-2.86 (m, 2H), 2.83-2.69 (m, 6H), 2.56 (d, J=6.3 Hz, 2H), 1.84-1.74 (m, 4H). LCMS (m/z): 395.1 (M+1).

Compound 66

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(naphthalen-1-yloxy)acetamide

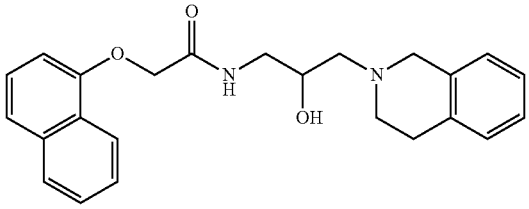


Step 1: ethyl 2-(naphthalen-1-yloxy)acetate



To a stirred mixture of naphthalen-1-ol (196 mg, 1.35 mmol) in MeCN (5 mL) was added ethyl bromoacetate (269 mg, 1.62 mmol) and K_2CO_3 (372 mg, 2.70 mmol). The mixture was stirred at 80° C. for 4 hours. The mixture was filtered and the filtrate concentrated. The residue was used directly for the next step without further purification (300 mg, Yield 95%).

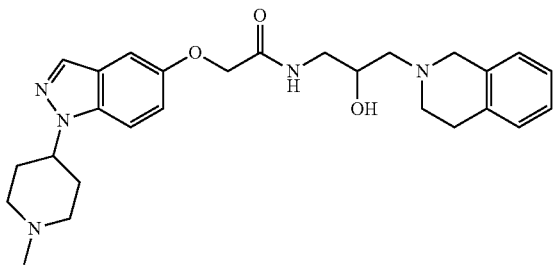
Step 2: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(naphthalen-1-yloxy)acetamide



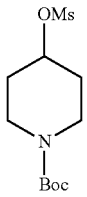
To a stirred mixture of ethyl 2-(naphthalen-1-yloxy)acetate (150 mg, 0.641 mmol) in EtOH (2 mL) was added 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (132 mg, 0.641 mmol). The mixture was stirred at 120° C. for 30 minutes under microwave mediated heating. After evaporation of the solvent, the reaction mixture was purified by prep-HPLC to afford the desired product (64 mg, Yield 25%). ^{1}H NMR (400 MHz, METHANOL-d_4) δ=8.41-8.31 (m, 1H), 7.90-7.80 (m, 1H), 7.58-7.46 (m, 3H), 7.44-7.35 (m, 1H), 7.18-6.95 (m, 5H), 6.91 (d, J=7.8 Hz, 1H), 4.76 (s, 2H), 4.05 (quin, J=6.0 Hz, 1H), 3.72-3.59 (m, 2H), 3.56-3.48 (m, 1H), 3.41 (dd, J=6.5, 13.6 Hz, 1H), 2.93-2.83 (m, 2H), 2.80-2.72 (m, 2H), 2.59-2.52 (m, 2H). LCMS (m/z): 391.2 (M+1).

Compound 71

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((1-(1-methylpiperidin-4-yl)-1H-indazol-5-yl)oxy)acetamide



Step 1: tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate

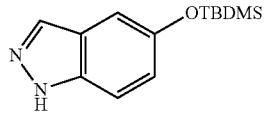


To a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (3.0 g, 14.9 mmol) in DCM (30 mL) was added triethylamine (4.5 g, 44.8 mmol). To this mixture methanesulfonyl chloride (5.1 g, 44.8 mmol) was added dropwise. After addition, the mixture was stirred at 25° C. for 3 h and then filtered. The filtrate was washed with aqueous HCl, dried over Na_2SO_4, and concentrated under reduced pressure to give tert-butyl 4-((methylsulfonyl)oxy) piperidine-1-carboxylate (3.58 g, yield 86%) as a white solid. This material was used in the next step without further purification. LCMS (m/z): 280.2 $[M+H]^+$.

^{1}H NMR (400 MHz, CDCl3) δ ppm 4.75-4.82 (m, 1H) 3.60-3.71 (m, 2H) 3.21-3.32 (m, 2H) 2.95 (s, 3H) 1.78-1.85 (m, 2H) 1.67-1.78 (m, 2H) 1.35 (s, 9H)

Step 2

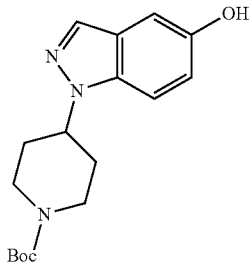
5-((tert-butyldimethylsilyl)oxy)-1H-indazole



To a solution of 1H-indazol-5-ol (400 mg, 2.98 mmol) in DMF (10 mL) was added TBDMSCl (537 mg, 3.58 mmol) and imidazole (405 mg, 5.96 mmol) at 0° C. and the resulting mixture was stirred at 25° C. for 16 h. The reaction was quenched by addition of water and the product extracted with ethyl acetate. The organic phase was washed with brine, then dried over Na_2SO_4, and concentrated under reduced pressure to give 5-((tert-butyldimethylsilyl)oxy)-1H-indazole (500 mg, yield 68%) as a brown solid, which was used in the next step without further purification. LCMS (m/z): 249.1 $[M+H]^+$

Step 3

tert-butyl 4-(5-hydroxy-1H-indazol-1-yl)piperidine-1-carboxylate

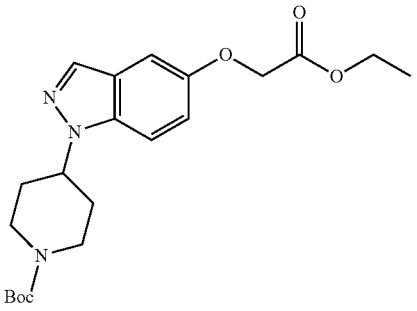


To a solution of NaH (60% in mineral oil) (43.5 mg, 1.81 mmol) in DMF at 0° C. was added 5-((tert-butyldimethylsilyl)oxy)-1H-indazole (300 mg, 1.21 mmol), and the mixture was stirred at 0° C. for 15 min. Tert-butyl 4-((methylsulfonyl) oxy) piperidine-1-carboxylate (243 mg, 1.21 mmol) was then added to the mixture at 0° C. After addition, the mixture was stirred at 85° C. for 12 h. The mixture was poured into water, and the product extracted with ethyl acetate. The organic phase was washed with water, dried over Na_2SO_4, concentrated under reduced pressure, and purified by TLC (Pet.Ether:EtOAc=2:1) to give tert-butyl 4-(5-hydroxy-1H-indazol-

1-yl) piperidine-1-carboxylate (250 mg, yield 65%) as a colorless oil. LCMS (m/z): 318.2 $[M+H]^+$

Step 4

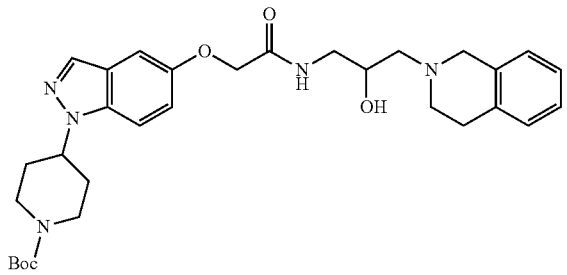
tert-butyl 4-(5-(2-ethoxy-2-oxoethoxy)-1H-indazol-1-yl)piperidine-1-carboxylate



To a solution of tert-butyl 4-(5-hydroxy-1H-indazol-1-yl) piperidine-1-carboxylate (150 mg, 0.458 mmol) in DMF (10 mL) at 0° C. was added NaH (60% in mineral oil) (16.8 mg, 0.706 mmol) and ethyl 2-bromoacetate (119 mg, 0.706 mmol). The mixture was stirred at 25° C. for 3 h, poured into water, and the product extracted with ethyl acetate. The organic phase was washed with water, dried over Na_2SO_4, concentrated under reduced pressure and purified by TLC (Pet.Ether:EtOAc=1:1) to give tert-butyl 4-(5-(2-ethoxy-2-oxoethoxy)-1H-indazol-1-yl)piperidine-1-carboxylate (120 mg, yield 65%) as a colorless oil. LCMS (m/z): 404.2 $[M+H]^+$

Step 5

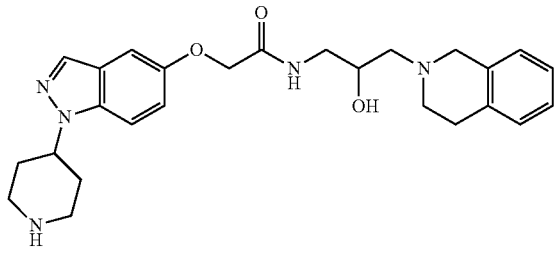
tert-butyl 4-(5-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)amino)-2-oxoethoxy)-1H-indazol-1-yl)piperidine-1-carboxylate



To a solution of tert-butyl 4-(5-(2-ethoxy-2-oxoethoxy)-1H-indazol-1-yl)piperidine-1-carboxylate (100 mg, 0.248 mmol) in EtOH (2 mL) was added 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (102.2 mg, 0.496 mmol) and the mixture was stirred at 120° C. for 2 h in microwave under N_2. The mixture was allowed to cool, concentrated under reduced pressure, purified by TLC (Pet.Ether:EtOAc=1:1) to give tert-butyl 4-(5-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)amino)-2-oxoethoxy)-1H-indazol-1-yl)piperidine-1-carboxylate (70 mg, yield 50%) as a colorless oil. LCMS (m/z): 564.3 $[M+H]^+$

Compound 70

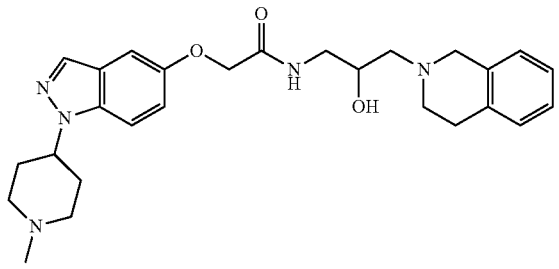
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((1-(piperidin-4-yl)-1H-indazol-5-yl)oxy) acetamide



To tert-butyl 4-(5-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)amino)-2-oxoethoxy)-1H-indazol-1-yl)piperidine-1-carboxylate (110 mg, 0.195 mmol) was added EtOAc.HCl (10 mL), the solution was stirred at 25° C. for 2 h, concentrated under reduced pressure, and purified by prep-HPLC to give N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((1-(piperidin-4-yl)-1H-indazol-5-yl) oxy)acetamide (85 mg, yield 94%) as a colorless oil. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 8.47 (br. s., 2H), 8.00 (s, 1H), 7.70 (d, J=8.78 Hz, 1H), 7.29-7.19 (m, 3H), 7.18-7.11 (m, 2H), 6.93 (dd, J=8.85, 1.95 Hz, 1H), 5.12 (s, 2H), 4.86-4.81 (m, 1H), 4.17 (s, 3H), 3.49-3.35 (m, 4H), 3.32-3.20 (m, 4H), 3.13-2.92 (m, 4H), 2.28-2.04 (m, 4H). LCMS (m/z): 464.2 $[M+H]^+$

Compound 71

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((1-(1-methylpiperidin-4-yl)-1H-indazol-5-yl)oxy)acetamide

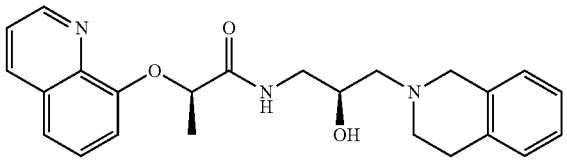


To a solution of N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((1-(piperidin-4-yl)-1H-indazol-5-yl) oxy)acetamide (50 mg, 0.108 mmol) in MeOH (5 mL) was added triethylamine (1 mL), HCHO (30%)(0.3 mL), and HOAC (0.4 mL). The mixture was stirred at 25° C. for 30 min, then $NaBH_3CN$ (0.4 mg) was added, and the mixture was stirred at 25° C. for an additional 1 h, concentrated under reduced pressure, and purified by prep-HPLC to give N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((1-(1-methylpiperidin-4-yl)-1H-indazol-5-yl)oxy)acetamide (51.1 mg, yield 99%) as a colorless oil. ^1H NMR (400 MHz,

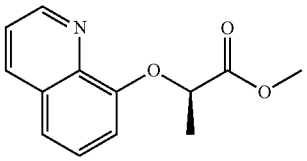
METHANOL-d_4) δ ppm 8.50 (br. s., 2H), 8.00 (s, 1H), 7.70 (d, J=8.78 Hz, 1H), 7.28-7.19 (m, 3H), 7.17-7.11 (m, 2H), 6.94 (dd, J=8.85, 1.82 Hz, 1H), 5.12 (s, 2H), 4.82 (br. s., 2H), 4.24-4.11 (m, 3H), 3.47-3.35 (m, 3H), 3.32 (br. s., 1H), 3.13-2.94 (m, 4H), 2.87 (s, 3H), 2.32-2.07 (m, 4H). LCMS (m/z): 478.3 $[M+H]^+$

Compound 73

(R)—N—((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(quinolin-8-yloxy)propanamide

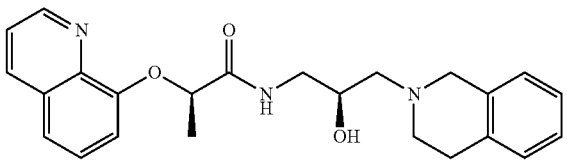


Step 1: (R)-Methyl 2-(quinolin-8-yloxy)propanoate



To a stirred mixture of quinolin-8-ol (300 mg, 2.07 mmol) in THF (5 mL) was added (S)-methyl 2-hydroxypropanoate (215 mg, 2.07 mmol), PPh_3 (647 mg, 2.47 mmol) and DEAD (430 mg, 2.47 mmol). The mixture was stirred at 25° C. for 16 hours. Subsequently, 1M HCl was added (10 mL) and the solution was washed with EtOAc (20 mL×3). The pH of the aqueous solution was raised by addition of aqueous $NaHCO_3$ (10 mL), and then this solution was washed with EtOAc (10 mL×3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica column chromatography to afford the product as a colorless oil (300 mg, 62.5% yield). LCMS (m/z): 233.1 $[M+H]^+$

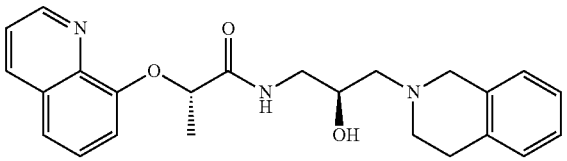
Step 2: (R)—N—((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(quinolin-8-yloxy)propanamide



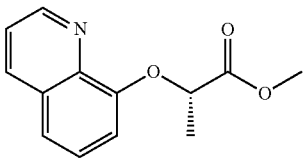
To a stirred mixture of (R)-methyl 2-(quinolin-8-yloxy)propanoate (100 mg, 0.433 mmol) in EtOH (1 mL) was added (R)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl) propan-2-ol (89.2 mg, 0.433 mmol). The mixture was stirred in a sealed tube in a microwave apparatus at 120° C. for 0.5 hour. After cooling to room temperature the solvent was evaporated, and the residue was first purified by prep-TLC and then prep-HPLC to afford the title compound (90 mg, yield: 51%). ^1H NMR (400 MHz, METHANOL-d_4)[8] ppm 8.89 (br. S., 1H), 8.29-8.42 (m, 1H), 7.49-7.65 (m, 3H), 7.28 (d, J=5.52 Hz, 1H), 6.89-7.13 (m, 4H), 5.01-5.13 (m, 1H), 4.10-3.84 (m, 1H), 3.45-3.60 (m, 2H), 3.35-3.43 (m, 2H), 2.81 (d, J=3.01 Hz, 2H), 2.65 (br. S., 2H), 2.34-2.49 (m, 2H) 1.71 (d, J=6.78 Hz, 3H), LCMS (m/z): 406.2 $[M+H]^+$

Compound 76

(S)—N—((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(quinolin-8-yloxy)propanamide

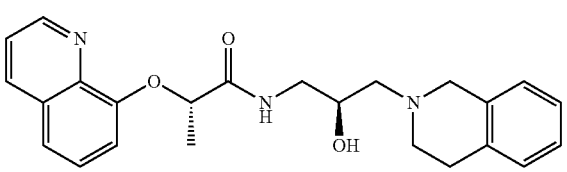


Step 1: (S)-methyl 2-(quinolin-8-yloxy)propanoate



To a stirred mixture of quinolin-8-ol (300 mg, 2.07 mmol) in THF (5 mL) was added (R)-methyl 2-hydroxypropanoate (215 mg, 2.07 mmol), PPh_3 (647 mg, 2.47 mmol) and DEAD (430 mg, 2.47 mmol). The mixture was stirred at 25° C. for 16 hours. Subsequently, 1M HCl was added (10 mL) and the solution was washed with EtOAc (20 mL×3). The pH of the aqueous solution was raised by addition of aqueous $NaHCO_3$ (10 mL), and then this solution was washed with EtOAc (10 mL×3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was directly for the next step. LCMS (m/z): 232.1/233.1 $[M+H]^+$

Step 2: (S)—N—((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(quinolin-8-yloxy)propanamide

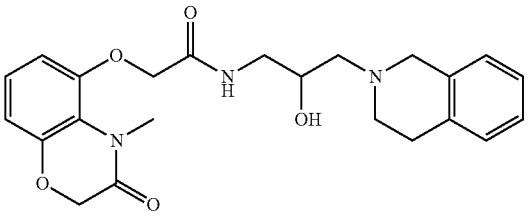


To a stirred mixture of (S)-methyl 2-(quinolin-8-yloxy)propanoate (100 mg, 0.433 mmol) in EtOH (1 mL) was added (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (89.2 mg, 0.433 mmol). The mixture was stirred in a sealed tube in a microwave apparatus at 120° C. for 0.5 hour. After

cooling to room temperature the solvent was evaporated, and the residue was first purified by prep-TLC and then prep-HPLC to afford the title compound (49 mg, yield: 28%). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.86-8.97 (m, 1H), 8.38 (d, J=7.03 Hz, 1H), 7.51-7.67 (m, 3H), 7.30 (d, J=7.28 Hz, 1H), 7.06-7.13 (m, 3H), 6.98 (d, J=6.53 Hz, 1H), 5.07 (q, J=6.53 Hz, 1H), 4.10-3.88 (m, 1H), 3.65-3.76 (m, 2H), 3.43-3.51 (m, 1H), 3.35 (br. s., 1H), 2.86 (dd, J=16.06, 3.76 Hz, 4H), 2.62 (d, J=6.02 Hz, 2H), 1.71 (d, J=6.53 Hz, 3H). LCMS (m/z): 406.2 $[M+H]^+$

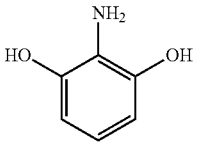
Compound 80

N-(3-(3,4-Dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yloxy)acetamide



Step 1

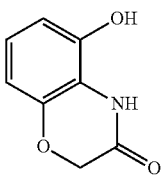
2-Aminobenzene-1,3-diol



A solution of 2-nitrobenzene-1,3-diol (5.00 g, 32.2 mmol) in MeOH (100 mL) was stirred under H_2 atmosphere (balloon) in the presence of 10% Pd/C (200 mg) for 16 h at room temperature. The reaction mixture was filtered and the filtrate was concentrated to render a residue characterized as 2-aminobenzene-1,3-diol (3.0 g, 95% yield), used as such for the next reaction step.

Step 2

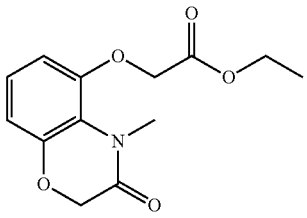
5-Hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-one



A stirred solution of 2-aminobenzene-1,3-diol (2.0 g, 16.0 mmol) and TEA (1.94 g, 19.2 mmol) in anhydrous DMF (30 mL) was treated with 2-chloroacetyl chloride (1.81 g, 16.0 mmol) and stirring continued for 16 h at room temperature, then K_2CO_3 (2.65 g, 19.2 mmol) was added and the mixture further stirred for 16 h at the same temperature. The reaction mixture was diluted with DCM (100 mL), washed twice with water and then with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The resulting residue was purified by chromatographic column of silicagel to give desired product (1.7 g, 64% yield) LCMS (m/z): 166.1 $[M+H]^+$.

Step 3

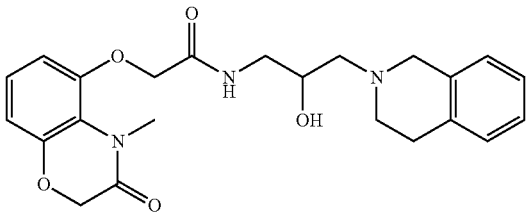
Ethyl 2-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yloxy)acetate



A stirred mixture of 5-hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-one (100 mg, 0.604 mmol) and K_2CO_3 (167 mg, 1.21 mmol) in anhydrous DMF (5 mL) was treated with ethyl 2-bromoacetate (121 mg, 0.727 mmol) and stirring continued at room temperature for 16 h. To this solution of crude ethyl 2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yloxy)acetate was added K_2CO_3 (39.6 mg, 0.287 mmol) followed by MeI (40.7 mg, 0.287 mmol). After being stirred at room temperature for 16 h, the reaction mixture was partitioned between water (50 mL) and DCM (100 mL). The organic layer was washed by water followed by and brine, dried over anhydrous Na_2SO_4, filtered and concentrated and the resulting residue was purified by preparative TLC to give desired product (43 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 6.99 (t, J=8.3 Hz, 1H), 6.74 (d, J=7.5 Hz, 1H), 6.55 (d, J=8.3 Hz, 1H), 4.69 (s, 2H), 4.51 (s, 2H), 4.30 (q, J=7.2 Hz, 2H), 3.56 (s, 3H), 1.34-1.33 (m, 1H), 1.33 (t, J=7.2 Hz, 3H)

Step 4

N-(3-(3,4-Dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yloxy)acetamide



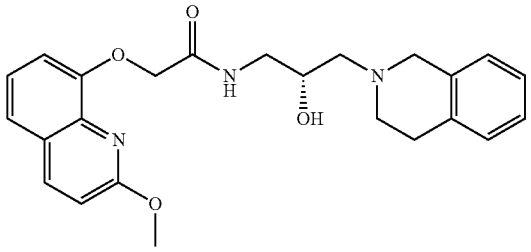
A reaction vessel containing a mixture of ethyl 2-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yloxy) acetate (43.0 mg, 0.162 mmol), 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl) propan-2-ol (33.0 mg, 0.163 mmol) and EtOH (0.5 mL) was placed in a microwave reactor and the mixture irradiated at external temperature of 120° C. for 1 h.

The reaction mixture was purified in two steps by preparative TLC followed by preparative HPLC to render the title product (19.2 mg, 19% yield)

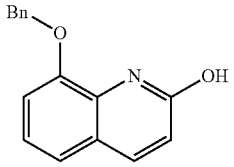
^{1}H NMR (400 MHz, METHANOL) δ ppm: 8.44 (br. s., 1H), 7.31-7.19 (m, 3H), 7.16 (d, J=6.5 Hz, 1H), 7.05 (t, J=1.0 Hz, 1H), 6.76 (dd, J=3.0, 8.3 Hz, 2H), 4.76-4.63 (m, 2H), 4.55-4.43 (m, 2H), 4.33-4.17 (m, 3H), 3.50 (s, 3H), 3.46-3.36 (m, 4H), 3.17-3.00 (m, 4H). LCMS (m/z): 426.2 $[M+H]^+$.

Compound 98

(R)—N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((2-methoxyquinolin-8-yl)oxy) acetamide

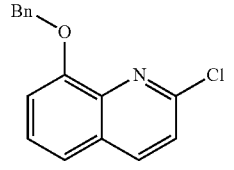


Step 1: 8-(benzyloxy)quinolin-2-ol



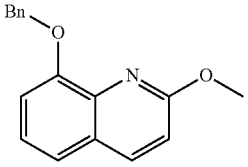
To a solution of quinoline-2,8-diol (5.0 g, 31.1 mmol) in i-PrOH (50 mL) was added BnBr (5.31 g, 31.1 mmol) and DBU (2.02 g, 5.32 mmol). The mixture was stirred at 80° C. for 16 h. The mixture was evaporated and to the residue was added DCM (100 mL), and this solution was washed with 0.5 N NaOH (50 mL), 10% HCl (50 mL), and H_2O (50 mL). The organic layer was evaporated to give the desired compound (6.6 g, yield 85%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 9.16 (br. s., 1H), 7.74 (d, J=9.8 Hz, 1H), 7.49-7.36 (m, 5H), 7.20-7.10 (m, 2H), 7.09-7.03 (m, 1H), 6.67 (d, J=9.5 Hz, 1H), 5.19 (s, 2H).

Step 2: 8-(benzyloxy)-2-chloroquinoline



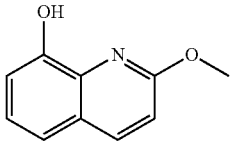
8-(benzyloxy)quinolin-2-ol (6.6 g, 26.3 mmol) was dissolved in $POCl_3$ (50 mL). The mixture was stirred at 90° C. for 16 h. The $POCl_3$ was evaporated and to the residue was added EtOAc (100 mL) and the solution was washed with a.q. $NaHCO_3$ (80 mL) and H_2O (80 mL). The EtOAc was removed under vacuum to give the desired compound (6.0 g, yield 85%). LCMS (m/z): 270.1 $[M+H]^+$

Step 3: 8-(benzyloxy)-2-methoxyquinoline



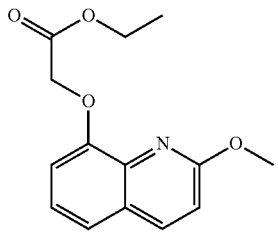
To a solution of MeONa (400 mg, 7.43 mmol) in MeOH (20 mL) was added 8-(benzyloxy)-2-chloroquinoline (2.0 g, 7.43 mmol). The mixture was stirred at 70° C. for 16 h. To the mixture was added H_2O (20 mL) and the product extracted with toluene (30 mL×3). The combined organic layers were dried with Na_2SO_4 and evaporated to give the desired compound (1.5 g, yield 79%). LCMS (m/z): 266.1 $[M+H]^+$

Step 4: 2-methoxyquinolin-8-ol



To a solution of 8-(benzyloxy)-2-methoxyquinoline (2.2 g, 8.3 mmol) in EtOH (40 mL) was added Pd/C (230 mg). The mixture was stirred at 25° C. for 16 h under an atmosphere of H_2. The mixture was filtered, and the filtrate was evaporated to give the desired compound (1.2 g, 83%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.91 (d, J=8.8 Hz, 1H), 7.52 (br. s., 1H), 7.23-7.15 (m, 2H), 7.07 (dd, J=1.4, 7.2 Hz, 1H), 6.85 (d, J=8.8 Hz, 1H), 3.99 (s, 3H).

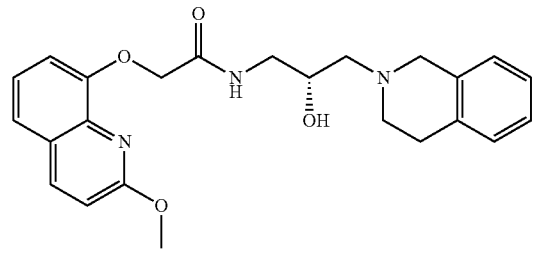
Step 5: ethyl 2-((2-methoxyquinolin-8-yl)oxy)acetate



To a solution of 2-methoxyquinolin-8-ol (500 mg, 2.86 mmol) in MeCN (10 mL) was added ethyl 2-bromoacetate (501 mg, 3.0 mmol) and K_2CO_3 (789 mg, 5.72 mmol). The mixture was stirred at 80° C. for 5 h. The mixture was filtered

and the filtrate evaporated to give the desired compound (700 mg, yield 94%). LCMS (m/z): 262.1 $[M+H]^+$

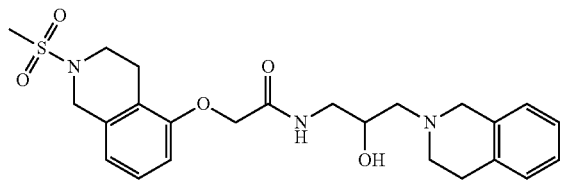
Step 6: (R)—N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((2-methoxyquinolin-8-yl)oxy)acetamide



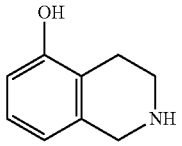
Ethyl 2-((2-methoxyquinolin-8-yl)oxy)acetate (100 mg, 0.383 mmol), (R)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (79.0 mg, 0.383 mmol) and EtOH (1 mL) were combined in a sealed tube. The mixture was stirred at 120° C. for 30 min in a microwave. The EtOH was evaporated and the residue was purified by pre-HPLC to give the desired product (77 mg, yield 48%). ^1H NMR ($MeOD-d_4$, 400 MHz) δ: 8.36 (br. s., 1H), 8.16 (d, J=8.8 Hz, 1H), 7.51 (d, J=7.5 Hz, 1H), 7.36 (t, J=7.9 Hz, 1H), 7.28-7.15 (m, 4H), 7.12 (d, J=6.8 Hz, 1H), 7.03 (d, J=8.8 Hz, 1H), 4.82 (s, 2H), 4.23-4.16 (m, 3H), 4.10 (s, 3H), 3.54-3.48 (m, 1H), 3.47-3.40 (m, 1H), 3.38-3.33 (m, 2H), 3.13-2.98 (m, 4H). LCMS (m/z): 422.2 $[M+H]^+$

Compound 102

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)oxy)acetamide

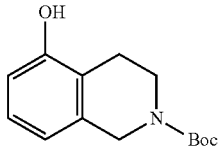


Step 1: 1,2,3,4-tetrahydroisoquinolin-5-ol



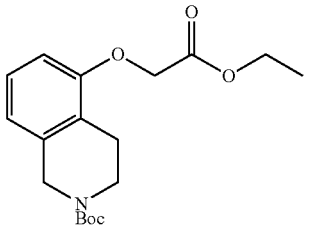
A mixture of isoquinolin-5-ol (4 g, 27.6 mmol) and PtO_2 (1.3 g) in HOAc (50 mL) was stirred under H_2 (45 Psi) at room temperature overnight. The mixture was filtered and the filtrate was concentrated under vacuum to give the crude product (3.2 g, 80%) which was used in the next step without purification. LCMS (m/z): 150.1 $[M+H]^+$.

Step 2: tert-butyl 3,4-dihydro-5-hydroxyisoquinoline-2(1H)-carboxylate



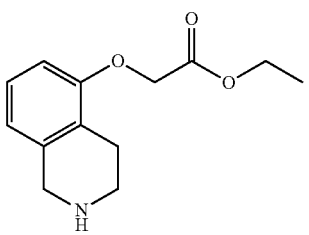
A mixture of 1,2,3,4-tetrahydroisoquinolin-5-ol (2.06 g, 13.8 mmol) and Na_2CO_3 (2.93 g, 27.6 mmol) in DMF was cooled with an ice-water bath. Then $(Boc)_2O$ (3.61 g, 16.6 mmol) was added in three portions. The solution was then stirred at room temperature overnight. The mixture was then filtered and the filtrate was concentrated under vacuum to give the crude product (3.1 g, 91%) which was used directly in the next step. LCMS (m/z): 250.2 $[M+H]^+$.

Step 3: tert-butyl 5-((ethoxycarbonyl)methoxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate



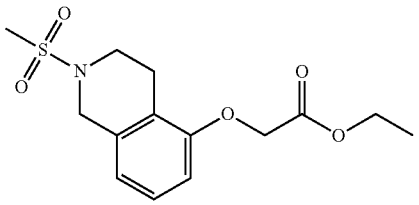
To a solution of tert-butyl 3,4-dihydro-5-hydroxyisoquinoline-2(1H)-carboxylate (750 mg, 3.01 mmol) and K_2CO_3 (498 mg, 3.61 mmol) in MeCN was added ethyl 2-bromoacetate (603 mg, 3.61 mmol). The mixture was stirred at room temperature overnight, the mixture was then filtered and the filtrate was concentrated under vacuum to give the desired product (900 mg, 90%). LCMS (m/z): 336.2 $[M+H]^+$.

Step 4: ethyl 2-((1,2,3,4-tetrahydroisoquinolin-5-yl)oxy)acetate



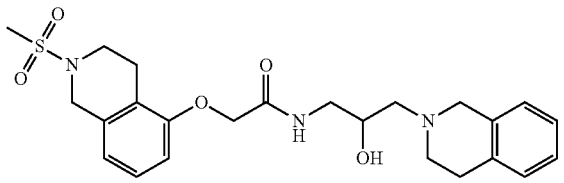
To a solution of tert-butyl 5-(2-ethoxy-2-oxoethoxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate (400 mg, 1.19 mmol) in ethyl acetate (10 mL), cooled in an ice-water bath, was added (10 mL, 1N) drop wise. The mixture was stirred at 25° C. for 16 h and then concentrated under vacuum to give the crude product (275 mg, 98%) which was used to the next step without further purification.

Step 5: ethyl 2-((2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)oxy)acetate



To a solution of ethyl 2-((1,2,3,4-tetrahydroisoquinolin-5-yl)oxy)acetate (300 mg, 1.28 mmol) and Et_3N (387 mg, 3.83 mmol) in DCM (25 mL) cooled in an ice-water bath was added MsCl (176.6 mg, 1.54 mmol) drop wise. The mixture was stirred at 25° C. for 16 h and then quenched with aq. NH_4Cl. The mixture was extracted with ethyl acetate and the combined organic layers were concentrated under vacuum to give the crude product (312 mg, 78%) which was used to the next step without purification.

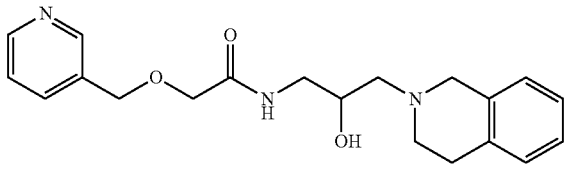
Step 6: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)oxy)acetamide



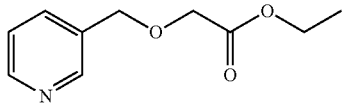
A mixture of ethyl 2-((2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)oxy)acetate (140 mg, 0.447 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (184 mg, 0.89 mmol) in EtOH (0.2 mL) was stirred at 120° C. for 30 min under microwave conditions. The mixture was diluted with MeOH and purified by prep-HPLC to afford N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-((2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)oxy)acetamide (53.5 mg, 25%). ^1H NMR (400 MHz, MeOD) δ 0.84 (s, 1H), 7.29-7.15 (m, 5H), 6.80 (d, J=8.2 Hz, 1H), 6.83 (d, J=7.7 Hz, 1H), 4.61 (s, 2H), 4.41 (s, 2H), 4.35-4.17 (m, 3H), 3.54 (t, J=6.1 Hz, 2H), 3.48-3.38 (m, 4H), 3.17-3.04 (m, 4H), 2.98 (t, J=6.0 Hz, 2H), 2.92 (s, 3H). LCMS (m/z): 474.2 $[M+H]^+$.

Compound 152

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(pyridin-3-ylmethoxy)acetamide

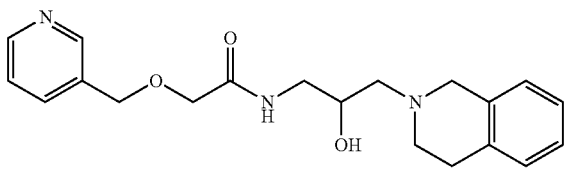


Step 1: Ethyl 2-(pyridin-3-ylmethoxy)acetate



To a solution of NaH (330 mg, 13.7 mmol) in DMF (10 mL) was added pyridin-3-ylmethanol (500 mg, 4.6 mmol) and the solution was stirred at 27° C. for 20 minutes. Ethyl 2-bromoacetate (921.8 mg, 5.52 mmol) was then added and the reaction mixture stirred at 27° C. for further 16 h. Once the reaction was complete by TLC analysis, the mixture was quenched by addition of water (50 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the Ethyl 2-(pyridin-3-ylmethoxy)acetate (600 mg, 66.8%) as colorless oil which was used in next step without further purification. LCMS: 196.1 $[M+H]^+$.

Step 2: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(pyridin-3-ylmethoxy)acetamide

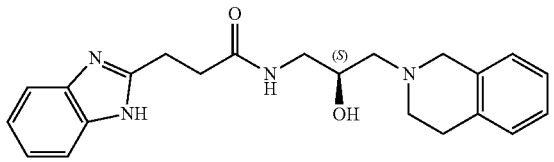


To a solution of Ethyl 2-(pyridin-3-ylmethoxy)acetate (100 mg, 0.51 mmol) in EtOH (0.5 ml) was added 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (105 mg, 0.51 mmol) at 28° C. The mixture was stirred at 120° C. under microwave heating for 1 hour until the reaction was com-

pleted by TLC. After evaporation of the solvent, the residue was purified by HPLC separation to give the title compound (30 mg, yield: 16.5%) as a white solid. LCMS: 356.2 $[M+H]^+$. ^1H NMR (MeOD, 400 MHz) δ 8.53 (s, 1H), 8.50 (d, J=4.8 Hz, 1H), 7.85 (d, J=8.0 Hz, 1H), 7.462 (dd, J_1=4.8 Hz, J_2=8.0 Hz, 1H), 7.19-7.03 (m, 4H), 4.58 (s, 2H), 4.02 (br. s, 3H), 3.72 (s, 2H), 3.42-3.36 (m, 2H), 2.93-2.83 (m, 4H), 2.62-2.61 (m, 2H).

Compound 175

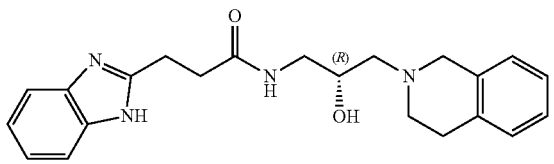
Step 1: (S)-3-(1H-benzo[d]imidazol-2-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)propanamide



To a solution of 3-(1H-benzo[d]imidazol-2-yl)propanoic acid (300 mg, 1.579 mmol) in DCM (10 mL) was added HATU (722 mg, 1.895 mmol) and TEA (478 mg, 4.737 mmol). After stirring for 30 min at room temperature, (S)-1-amino-3-(3,4-dihydro isoquinolin-2(1H)-yl)propan-2-ol (488 mg, 2.368 mmol) was added and the resulting mixture then stirred at room temperature for 16 h. After completion of the reaction the solvent was evaporated at reduced pressure and the residue purified by preparative HPLC to give the title compound (159.1 mg, 26%). ^1H NMR (400 MHz, METHANOL-d_4) δ=7.51 (br. s., 2H), 7.22-7.16 (m, 2H), 7.13-7.06 (m, 3H), 7.02-6.97 (m, 1H), 3.98-3.90 (m, 1H), 3.66-3.55 (m, 2H), 3.37 (dd, J=4.9, 13.7 Hz, 1H), 3.25-3.17 (m, 3H), 2.89-2.83 (m, 2H), 2.79 (t, J=7.5 Hz, 2H), 2.74-2.69 (m, 2H), 2.50-2.45 (m, 2H). LCMS (m/z): 379.1 $[M+H]^+$.

Compound 192

Step 1: (R)-3-(1H-benzo[d]imidazol-2-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)propanamide



To a solution of 3-(1H-benzo[d]imidazol-2-yl)propanoic acid (300 mg, 1.579 mmol) in DCM (10 mL) was added HATU (722 mg, 1.895 mmol) and TEA (478 mg, 4.737 mmol). After stirring for 30 min at room temperature, (R)-1-amino-3-(3,4-dihydro isoquinolin-2(1H)-yl)propan-2-ol (488 mg, 2.368 mmol) was added and the resulting mixture then stirred at room temperature for 16 h. Once TLC analysis showed the reaction to be complete, the solvent was evaporated at reduced pressure and the residue purified by preparative HPLC to give the title compound (184.6 mg, 30.9%) as white solid. ^1H NMR (400 MHz, METHANOL-d_4) δ=7.56-7.46 (m, 2H), 7.22-7.17 (m, 2H), 7.13-7.07 (m, 3H), 7.02-6.97 (m, 1H), 3.94 (t, J=5.8 Hz, 1H), 3.61 (d, J=3.3 Hz, 2H), 3.40-3.35 (m, 1H), 3.25-3.18 (m, 3H), 2.89-2.84 (m, 2H), 2.79 (t, J=7.4 Hz, 2H), 2.74-2.69 (m, 2H), 2.47 (d, J=6.5 Hz, 2H). LCMS (m/z): 379.1 $[M+H]^+$.

Biological Assays

PRMT5 Biochemical Assay

General Materials.

S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), bicine, KCl, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), and Tris(2-carboxyethyl)phosphine hydrochloride solution (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ^3H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

Substrates.

Peptide representative of human histone H4 residues 1-15 was synthesized with a C-terminal linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptide was high high-performance liquid chromatography (HPLC) purified to greater than 95% purity and confirmed by liquid chromatography mass spectrometry (LC-MS). The sequence was Ac-SGRGKGGKGLGKGGA[K-Biot]-amide (SEQ ID NO.:3).

Molecular Biology:

Full-length human PRMT5 (NM_006109.3) transcript variant 1 clone was amplified from a fetal brain cDNA library, incorporating flanking 5' sequence encoding a FLAG tag (MDYKDDDDK) (SEQ ID NO.:4) fused directly to Ala 2 of PRMT5. Full-length human MEP50 (NM_024102) clone was amplified from a human testis cDNA library incorporating a 5' sequence encoding a 6-histidine tag (MHHHHHH) (SEQ ID NO.:5) fused directly to Arg 2 of MEP50. The amplified genes were subcloned into pENTR/D/TEV (Life Technologies) and subsequently transferred by Gateway™ attL×attR recombination to pDEST8 baculvirus expression vector (Life Technologies).

Protein Expression.

Recombinant baculovirus and Baculovirus-Infected Insect Cells (BIIC) were generated according to Bac-to-Bac kit instructions (Life Technologies) and Wasilko, 2006, respectively. Protein over-expression was accomplished by infecting exponentially growing *Spodoptera frugiperda* (SF9) cell culture at 1.2×10^6 cell/ml with a 5000 fold dilution of BIIC stock. Infections were carried out at 27° C. for 72 hours, harvested by centrifugation, and stored at −80° C. for purification.

Protein Purification.

Expressed full-length human Flag-PRMT5/6His-MeP50 protein complex was purified from cell paste by NiNTA aga-

rose affinity chromatography after a five hour equilibration of the resin with buffer containing 50 mM Tris-HCL, pH 8.0, 25 mM NaCl, and 1 mM TCEP at 4° C., to minimize the adsorption of tubulin impurity by the resin. Flag-PRMT5/6His-MeP50 was eluted with 300 mM Imidazole in the same buffer. The purity of recovered protein was 87%. Reference: Wasilko, D. J. and S. E. Lee: "TIPS: titerless infected-cells preservation and scale-up" Bioprocess J., 5 (2006), pp. 29-32.

Predicted Translations:

Flag-PRMT5

(SEQ ID NO.: 6)

MDYKDDDDKA AMAVGGAGGS RVSSGRDLNC VPEIADTLGA VAKQGFDFLC MPVFHPRFKR

EFIQEPAKNR PGPQTRSDLL LSGRDWNTLI VGKLSPWIRP DSKVEKIRRN SEAAMLQELN

FGAYLGLPAF LLPLNQEDNT NLARVLTNHI HTGHHSSMFW MRVPLVAPED LRDDIIENAP

TTHTEEYSGE EKTWMWWHNF RTLCDYSKRI AVALEIGADL PSNHVIDRWL GEPIKAAILP

TSIFLTNKKG FPVLSKMHQR LIFRLLKLEV QFIITGTNHH SEKEFCSYLQ YLEYLSQNRP

PPNAYELFAK GYEDYLQSPL QPLMDNLESQ TYEVFEKDPI KYSQYQQAIY KCLLDRVPEE

EKDTNVQVLM VLGAGRGPLV NASLRAAKQA DRRIKLYAVE KNPNAVVTLE NWQFEEWGSQ

VTVVSSDMRE WVAPEKADII VSELLGSFAD NELSPECLDG AQHFLKDDGV SIPGEYTSFL

APISSSKLYN EVRACREKDR DPEAQFEMPY VVRLHNFHQL SAPQPCFTFS HPNRDPMIDN

NRYCTLEFPV EVNTVLHGFA GYFETVLYQD ITLSIRPETH SPGMFSWFPI LFPIKQPITV

REGQTICVRF WRCSNSKKVW YEWAVTAPVC SAIHNPTGRS YTIG L

6His-MEP50

(SEQ ID NO.: 7)

MHHHHHHRKE TPPPLVPPAA REWNLPPNAP ACMERQLEAA RYRSDGALLL GASSLSGRCW

AGSLWLFKDP CAAPNEGFCS AGVQTEAGVA DLTWVGERGI LVASDSGAVE LWELDENETL

IVSKFCKYEH DDIVSTVSVL SSGTQAVSGS KDICIKVWDL AQQVVLSSYR AHAAQVTCVA

ASPHKDSVFL SCSEDNRILL WDTRCPKPAS QIGCSAPGYL PTSLAWHPQQ SEVFVFGDEN

GTVSLVDTKS TSCVLSSAVH SQCVTGLVFS PHSVPFLASL SEDCSLAVLD SSLSELFRSQ

AHRDFVRDAT WSPLNHSLLT TVGWDHQVVH HVVPTEPLPA PGPASVTE

General Procedure for PRMT5/MEP50 Enzyme Assays on Peptide Substrates.

The assays were all performed in a buffer consisting of 20 mM Bicine (pH=7.6), 1 mM TCEP, 0.005% BSG, and 0.002% Tween20, prepared on the day of use. Compounds in 100% DMSO (1 ul) were spotted into a polypropylene 384-well V-bottom plates (Greiner) using a Platemate Plus outfitted with a 384-channel head (Thermo Scientific). DMSO (1 ul) was added to Columns 11, 12, 23, 24, rows A-H for the maximum signal control and 1 ul of SAH, a known product and inhibitor of PRMT5/MEP50, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40 ul) containing the PRMT5/MEP50 enzyme and the peptide was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with PRMT5/MEP50 for 30 min at 25 degrees Celsius, then a cocktail (10 ul) containing ^{3}H-SAM was added to initiate the reaction (final volume=51 ul). The final concentrations of the components were as follows: PRMT5/MEP50 was 4 nM, ^{3}H-SAM was 75 nM, peptide was 40 nM, SAH in the minimum signal control wells was 100 uM, and the DMSO concentration was 1%. The assays were stopped by the addition of non-radioactive SAM (10 ul) to a final concentration of 600 uM, which dilutes the ^{3}H-SAM to a level where its incorporation into the peptide substrate is no longer detectable. 50 ul of the reaction in the 384-well polypropylene plate was then transferred to a 384-well Flashplate and the biotinylated peptides were allowed to bind to the streptavidin surface for at least 1 hour before being washed three times with 0.1% Tween20 in a Biotek ELx405 plate washer. The plates were then read in a PerkinElmer TopCount plate reader to measure the quantity of ^{3}H-labeled peptide bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\% \ inh = 100 - \left(\frac{dpm_{cmpd} - dpm_{min}}{dpm_{max} - dpm_{min}}\right) \times 100$$

Where dpm=disintegrations per minute, cmpd=signal in assay well, and min and max are the respective minimum and maximum signal controls.

Four-parameter *IC50* fit

$$Y = \text{Bottom} + \frac{(\text{Top} - \text{Bottom})}{\left(1 + \left(\frac{X}{IC_{50}}\right)^{Hill\ Coefficient}\right)}$$

Where top and bottom are the normally allowed to float, but may be fixed at 100 or 0 respectively in a 3-parameter fit. The Hill Coefficient normally allowed to float but may also be fixed at 1 in a 3-parameter fit. Y is the % inhibition and X is the compound concentration.

Z-138 Methylation Assay

Z-138 suspension cells were purchased from ATCC (American Type Culture Collection, Manassas, Va.). RPMI/

Glutamax medium, penicillin-streptomycin, heat inactivated fetal bovine serum, and D-PBS were purchased from Life Technologies, Grand Island, N.Y., USA. Odyssey blocking buffer, 800CW goat anti-rabbit IgG (H+L) antibody, and Licor Odyssey infrared scanner were purchased from Licor Biosciences, Lincoln, Nebr., USA. Symmetric di-methyl arginine antibody was purchased from EMD Millipore, Billerica, Mass., USA. 16% Paraformaldehyde was purchased from Electron Microscopy Sciences, Hatfield, Pa., USA.

Z-138 suspension cells were maintained in growth medium (RPMI 1640 supplemented with 10% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) and cultured at 37° C. under 5% CO_2.

Cell Treatment, in Cell Western (ICW) for Detection of Symmetric Di-Methyl Arginine and DNA Content.

Z-138 cells were seeded in assay medium at a concentration of 50,000 cells per mL to a 384-well cell culture plate with 50 μL per well. Compound (100 nL) from 384 well source plates was added directly to 384 well cell plate. Plates were incubated at 37° C., 5% CO_2 for 96 hours. After four days of incubation, 40 μL of cells from incubated plates were added to poly-D-lysine coated 384 well culture plates (BD Biosciences 356697). Plates were incubated at room temperature for 30 minutes then incubated at 37° C., 5% CO_2 for 5 hours. After the incubation, 40 μL per well of 8% paraformaldehyde in PBS (16% paraformaldahyde was diluted to 8% in PBS) was added to each plate and incubated for 30 minutes. Plates were transferred to a Biotek 405 plate washer and washed 5 times with 100 μL per well of wash buffer (1×PBS with 0.1% Triton X-100 (v/v)). Next 30 μL per well of Odyssey blocking buffer were added to each plate and incubated 1 hour at room temperature. Blocking buffer was removed and 20 μL per well of primary antibody was added (symmetric di-methyl arginine diluted 1:100 in Odyssey buffer with 0.1% Tween 20 (v/v)) and plates were incubated overnight (16 hours) at 4° C. Plates were washed 5 times with 100 μL per well of wash buffer. Next 20 μL per well of secondary antibody was added (1:200 800CW goat anti-rabbit IgG (H+L) antibody, 1:1000 DRAQ5 (Biostatus limited) in Odyssey buffer with 0.1% Tween 20 (v/v)) and incubated for 1 hour at room temperature. The plates were washed 5 times with 100 μL per well wash buffer then 1 time with 100 μL per well of water. Plates were allowed to dry at room temperature then imaged on the Licor Odyssey machine which measures integrated intensity at 700 nm and 800 nm wavelengths. Both 700 and 800 channels were scanned.

Calculations:

First, the ratio for each well was determined by:

$$\left(\frac{\text{symmetric di-methyl Arginine 800 nm value}}{DRAQ5\ 700\ \text{nm value}}\right)$$

Each plate included fourteen control wells of DMSO only treatment (minimum inhibition) as well as fourteen control wells for maximum inhibition treated with 3 μM of a reference compound (Background wells). The average of the ratio values for each control type was calculated and used to determine the percent inhibition for each test well in the plate. Reference compound was serially diluted three-fold in DMSO for a total of nine test concentrations, beginning at 3 μM. Percent inhibition was determined and IC_{50} curves were generated using triplicate wells per concentration of compound.

$$\text{Percent Inhibition} = 100 - \left(\left(\frac{(\text{Individual Test Sample Ratio}) - (\text{Background Avg Ratio})}{(\text{Minimum Inhibition Ratio}) - (\text{Background Average Ratio})}\right) * 100\right)$$

Z-138 Proliferation Assay

Z-138 suspension cells were purchased from ATCC (American Type Culture Collection, Manassas, Va.). RPMI/Glutamax medium, penicillin-streptomycin, heat inactivated fetal bovine serum were purchased from Life Technologies, Grand Island, N.Y., USA. V-bottom polypropylene 384-well plates were purchased from Greiner Bio-One, Monroe, N.C., USA. Cell culture 384-well white opaque plates were purchased from Perkin Elmer, Waltham, Mass., USA. Cell-Titer Glo® was purchased from Promega Corporation, Madison, Wis., USA. SpectraMax M5 plate reader was purchased from Molecular Devices LLC, Sunnyvale, Calif., USA.

Z-138 suspension cells were maintained in growth medium (RPMI 1640 supplemented with 10% v/v heat inactivated fetal bovine serum and cultured at 37° C. under 5% CO_2 Under assay conditions, cells were incubated in assay medium (RPMI 1640 supplemented with 10% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) at 37° C. under 5% CO_2.

For the assessment of the effect of compounds on the proliferation of the Z-138 cell line, exponentially growing cells were plated in 384-well white opaque plates at a density of 10,000 cells/ml in a final volume of 50 μl of assay medium. A compound source plate was prepared by performing triplicate nine-point 3-fold serial dilutions in DMSO, beginning at 10 mM (final top concentration of compound in the assay was 20 μM and the DMSO was 0.2%). A 100 nL aliquot from the compound stock plate was added to its respective well in the cell plate. The 100% inhibition control consisted of cells treated with 200 nM final concentration of staurosporine and the 0% inhibition control consisted of DMSO treated cells. After addition of compounds, assay plates were incubated for 5 days at 37° C., 5% CO_2, relative humidity >90%. Cell viability was measured by quantitation of ATP present in the cell cultures, adding 35 μl of Cell Titer Glo® reagent to the cell plates. Luminescence was read in the SpectraMax M5 microplate reader. The concentration of compound inhibiting cell viability by 50% was determined using a 4-parametric fit of the normalized dose response curves.

Results for certain compounds described herein are shown in Table 2.

TABLE 2

Biological Assay Results			
Cmpd No	Biochemical IC_{50}	ICW EC_{50}	Proliferation EC_{50}
1	B	B	—
2	C	—	—
3	C	—	—
4	A	—	—
5	D	—	—
6	A	A	B

TABLE 2-continued

Cmpd No	Biochemical IC_{50}	ICW EC_{50}	Proliferation EC_{50}
7	B	B	D
8	B	B	D
9	B	D	D
10	C	—	—
11	B	B	D
12	B	B	D
13	C	—	—
14	C	—	—
15	B	B	C
16	B	B	D
17	B	B	D
18	C	C	**
19	A	B	C
20	A	B	C
21	B	B	**
22	A	B	C
23	A	B	C
24	B	—	—
25	B	—	—
26	A	B	C
27	A	B	C
28	A	B	C
29	B	B	**
30	B	B	D
31	C	B	D
32	B	B	D
33	C	—	—
34	B	B	D
35	B	B	D
36	B	B	**
37	A	A	C
38	A	A	C
39	A	A	B
40	A	B	C
41	C	—	—
42	B	B	**
43	A	B	C
44	B	B	D
45	A	A	B
46	B	B	D
47	A	B	C
48	A	B	D
49	A	B	C
50	A	A	C
51	D	—	—
52	C	—	—
53	A	B	C
54	B	B	—
55	B	—	—
56	C	—	—
57	D	—	—
58	D	—	—
59	C	—	—
60	B	C	—
61	C	—	—
62	C	—	—
63	D	—	—
64	A	B	C
65	A	B	C
66	A	B	C
67	A	A	C
68	A	B	**
69	B	C	—
70	A	B	**
71	A	B	**
72	C	—	—
73	A	A	B
74	A	B	C
75	A	A	C
76	A	B	C
77	A	A	C
78	B	B	—
79	A	B	C
80	A	B	D
81	A	A	B
82	A	A	C

TABLE 2-continued

Cmpd No	Biochemical IC_{50}	ICW EC_{50}	Proliferation EC_{50}
83	B	B	D
84	A	B	C
85	C	C	—
86	A	B	D
87	C	—	—
88	A	B	D
89	B	C	—
90	A	B	D
91	A	B	C
92	A	A	C
93	A	A	C
94	A	B	D
95	A	B	D
96	A	B	D
97	B	B	C
98	A	A	C
99	A	B	C
100	A	A	C
101	A	A	C
102	A	A	C
103	A	B	**
104	B	C	**
105	A	B	C
106	B	B	**
107	A	A	C
108	A	B	D
109	A	A	B
110	A	A	B
111	A	A	B
112	B	B	**
113	B	B	D
114	B	C	**
115	D	—	—
116	C	C	**
117	B	B	C
118	B	C	**
119	A	B	D
120	B	C	**
121	C	—	—
122	B	C	**
123	A	B	C
124	C	C	**
125	C	—	—
126	E	—	—
127	B	C	**
128	E	—	—
129	B	C	**
130	A	B	C
131	C	—	—
132	C	—	—
133	*	—	—
134	B	C	**
135	C	—	—
136	C	—	—
137	B	C	**
138	B	C	—
139	*	—	—
140	C	—	—
141	C	—	—
142	B	B	**
143	C	—	—
144	*	—	—
145	C	—	—
146	A	B	—
147	*	—	—
148	*	—	—
149	A	B	—
150	B	—	—
151	B	—	—
152	C	—	—
153	A	B	D
154	C	—	—
155	A	A	C
156	C	—	—
157	C	—	—
158	A	B	C

TABLE 2-continued

Biological Assay Results			
Cmpd No	Biochemical IC_{50}	ICW EC_{50}	Proliferation EC_{50}
159	A	A	C
160	B	C	**
161	B	C	**
162	C	C	**
163	A	B	C
164	A	A	B
165	B	B	**
166	C	—	—
167	C	—	—
168	A	A	C
169	A	A	C
170	A	B	D
171	C	—	—
172	B	B	D
173	C	—	—
174	B	B	**
175	A	A	B
176	C	—	—
177	B	B	D
178	B	B	C
179	B	B	D
180	C	—	—
181	A	A	—
182	B	B	—
183	B	B	—
184	C	—	—

TABLE 2-continued

Biological Assay Results			
Cmpd No	Biochemical IC_{50}	ICW EC_{50}	Proliferation EC_{50}
185	B	—	—
186	C	—	—
187	C	—	—
188	C	—	—
189	B	—	—
190	A	—	—
191	A	—	—
192	B	—	—
193	C	—	—

For Table 2, "A" indicates an IC_{50} or EC_{50} < 0.100 μM, "B" indicates an IC_{50} or EC_{50} of 0.101-1.000 μM, "C" indicates an IC_{50} or EC_{50} of 1.001-10.000 μM, "D" indicates an IC_{50} or EC_{50} of 10.001-50 μM, and "E" indicates an IC_{50} or EC_{50} > 50 μM.
"—" indicates no data shown.
"*" indicates an IC_{50} or EC_{50} > 10 μM.
"**" indicates an IC_{50} or EC_{50} > 20 μM.

Other Embodiments

The foregoing has been a description of certain non-limiting embodiments of the invention. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 7

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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Met Ala Ala Met Ala Val Gly Gly Ala Gly Gly Ser Arg Val Ser Ser
1               5                  10                  15

Gly Arg Asp Leu Asn Cys Val Pro Glu Ile Ala Asp Thr Leu Gly Ala
            20                  25                  30

Val Ala Lys Gln Gly Phe Asp Phe Leu Cys Met Pro Val Phe His Pro
        35                  40                  45

Arg Phe Lys Arg Glu Phe Ile Gln Glu Pro Ala Lys Asn Arg Pro Gly
    50                  55                  60

Pro Gln Thr Arg Ser Asp Leu Leu Leu Ser Gly Arg Asp Trp Asn Thr
65                  70                  75                  80

Leu Ile Val Gly Lys Leu Ser Pro Trp Ile Arg Pro Asp Ser Lys Val
                85                  90                  95

Glu Lys Ile Arg Arg Asn Ser Glu Ala Ala Met Leu Gln Glu Leu Asn
            100                 105                 110

Phe Gly Ala Tyr Leu Gly Leu Pro Ala Phe Leu Leu Pro Leu Asn Gln
        115                 120                 125

Glu Asp Asn Thr Asn Leu Ala Arg Val Leu Thr Asn His Ile His Thr
    130                 135                 140

Gly His His Ser Ser Met Phe Trp Met Arg Val Pro Leu Val Ala Pro
145                 150                 155                 160

Glu Asp Leu Arg Asp Asp Ile Ile Glu Asn Ala Pro Thr Thr His Thr
                165                 170                 175
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Glu Glu Tyr Ser Gly Glu Glu Lys Thr Trp Met Trp Trp His Asn Phe
            180                 185                 190

Arg Thr Leu Cys Asp Tyr Ser Lys Arg Ile Ala Val Ala Leu Glu Ile
        195                 200                 205

Gly Ala Asp Leu Pro Ser Asn His Val Ile Asp Arg Trp Leu Gly Glu
    210                 215                 220

Pro Ile Lys Ala Ala Ile Leu Pro Thr Ser Ile Phe Leu Thr Asn Lys
225                 230                 235                 240

Lys Gly Phe Pro Val Leu Ser Lys Met His Gln Arg Leu Ile Phe Arg
                245                 250                 255

Leu Leu Lys Leu Glu Val Gln Phe Ile Ile Thr Gly Thr Asn His His
            260                 265                 270

Ser Glu Lys Glu Phe Cys Ser Tyr Leu Gln Tyr Leu Glu Tyr Leu Ser
        275                 280                 285

Gln Asn Arg Pro Pro Pro Asn Ala Tyr Glu Leu Phe Ala Lys Gly Tyr
    290                 295                 300

Glu Asp Tyr Leu Gln Ser Pro Leu Gln Pro Leu Met Asp Asn Leu Glu
305                 310                 315                 320

Ser Gln Thr Tyr Glu Val Phe Glu Lys Asp Pro Ile Lys Tyr Ser Gln
                325                 330                 335

Tyr Gln Gln Ala Ile Tyr Lys Cys Leu Leu Asp Arg Val Pro Glu Glu
            340                 345                 350

Glu Lys Asp Thr Asn Val Gln Val Leu Met Val Leu Gly Ala Gly Arg
        355                 360                 365

Gly Pro Leu Val Asn Ala Ser Leu Arg Ala Ala Lys Gln Ala Asp Arg
    370                 375                 380

Arg Ile Lys Leu Tyr Ala Val Glu Lys Asn Pro Asn Ala Val Val Thr
385                 390                 395                 400

Leu Glu Asn Trp Gln Phe Glu Glu Trp Gly Ser Gln Val Thr Val Val
                405                 410                 415

Ser Ser Asp Met Arg Glu Trp Val Ala Pro Glu Lys Ala Asp Ile Ile
            420                 425                 430

Val Ser Glu Leu Leu Gly Ser Phe Ala Asp Asn Glu Leu Ser Pro Glu
        435                 440                 445

Cys Leu Asp Gly Ala Gln His Phe Leu Lys Asp Asp Gly Val Ser Ile
    450                 455                 460

Pro Gly Glu Tyr Thr Ser Phe Leu Ala Pro Ile Ser Ser Ser Lys Leu
465                 470                 475                 480

Tyr Asn Glu Val Arg Ala Cys Arg Glu Lys Asp Arg Asp Pro Glu Ala
                485                 490                 495

Gln Phe Glu Met Pro Tyr Val Val Arg Leu His Asn Phe His Gln Leu
            500                 505                 510

Ser Ala Pro Gln Pro Cys Phe Thr Phe Ser His Pro Asn Arg Asp Pro
        515                 520                 525

Met Ile Asp Asn Asn Arg Tyr Cys Thr Leu Glu Phe Pro Val Glu Val
    530                 535                 540

Asn Thr Val Leu His Gly Phe Ala Gly Tyr Phe Glu Thr Val Leu Tyr
545                 550                 555                 560

Gln Asp Ile Thr Leu Ser Ile Arg Pro Glu Thr His Ser Pro Gly Met
                565                 570                 575

Phe Ser Trp Phe Pro Ile Leu Phe Pro Ile Lys Gln Pro Ile Thr Val
            580                 585                 590
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Arg Glu Gly Gln Thr Ile Cys Val Arg Phe Trp Arg Cys Ser Asn Ser
        595                 600                 605

Lys Lys Val Trp Tyr Glu Trp Ala Val Thr Ala Pro Val Cys Ser Ala
    610                 615                 620

Ile His Asn Pro Thr Gly Arg Ser Tyr Thr Ile Gly Leu
625                 630                 635


<210> SEQ ID NO 2
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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Met Arg Gly Pro Asn Ser Gly Thr Glu Lys Gly Arg Leu Val Ile Pro
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Glu Lys Gln Gly Phe Asp Phe Leu Cys Met Pro Val Phe His Pro Arg
            20                  25                  30

Phe Lys Arg Glu Phe Ile Gln Glu Pro Ala Lys Asn Arg Pro Gly Pro
        35                  40                  45

Gln Thr Arg Ser Asp Leu Leu Leu Ser Gly Arg Asp Trp Asn Thr Leu
    50                  55                  60

Ile Val Gly Lys Leu Ser Pro Trp Ile Arg Pro Asp Ser Lys Val Glu
65                  70                  75                  80

Lys Ile Arg Arg Asn Ser Glu Ala Ala Met Leu Gln Glu Leu Asn Phe
                85                  90                  95

Gly Ala Tyr Leu Gly Leu Pro Ala Phe Leu Leu Pro Leu Asn Gln Glu
            100                 105                 110

Asp Asn Thr Asn Leu Ala Arg Val Leu Thr Asn His Ile His Thr Gly
        115                 120                 125

His His Ser Ser Met Phe Trp Met Arg Val Pro Leu Val Ala Pro Glu
    130                 135                 140

Asp Leu Arg Asp Asp Ile Ile Glu Asn Ala Pro Thr Thr His Thr Glu
145                 150                 155                 160

Glu Tyr Ser Gly Glu Glu Lys Thr Trp Met Trp Trp His Asn Phe Arg
                165                 170                 175

Thr Leu Cys Asp Tyr Ser Lys Arg Ile Ala Val Ala Leu Glu Ile Gly
            180                 185                 190

Ala Asp Leu Pro Ser Asn His Val Ile Asp Arg Trp Leu Gly Glu Pro
        195                 200                 205

Ile Lys Ala Ala Ile Leu Pro Thr Ser Ile Phe Leu Thr Asn Lys Lys
    210                 215                 220

Gly Phe Pro Val Leu Ser Lys Met His Gln Arg Leu Ile Phe Arg Leu
225                 230                 235                 240

Leu Lys Leu Glu Val Gln Phe Ile Ile Thr Gly Thr Asn His His Ser
                245                 250                 255

Glu Lys Glu Phe Cys Ser Tyr Leu Gln Tyr Leu Glu Tyr Leu Ser Gln
            260                 265                 270

Asn Arg Pro Pro Pro Asn Ala Tyr Glu Leu Phe Ala Lys Gly Tyr Glu
        275                 280                 285

Asp Tyr Leu Gln Ser Pro Leu Gln Pro Leu Met Asp Asn Leu Glu Ser
    290                 295                 300

Gln Thr Tyr Glu Val Phe Glu Lys Asp Pro Ile Lys Tyr Ser Gln Tyr
305                 310                 315                 320

Gln Gln Ala Ile Tyr Lys Cys Leu Leu Asp Arg Val Pro Glu Glu Glu
                325                 330                 335
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Lys Asp Thr Asn Val Gln Val Leu Met Val Leu Gly Ala Gly Arg Gly
            340                 345                 350

Pro Leu Val Asn Ala Ser Leu Arg Ala Ala Lys Gln Ala Asp Arg Arg
        355                 360                 365

Ile Lys Leu Tyr Ala Val Glu Lys Asn Pro Asn Ala Val Val Thr Leu
    370                 375                 380

Glu Asn Trp Gln Phe Glu Glu Trp Gly Ser Gln Val Thr Val Val Ser
385                 390                 395                 400

Ser Asp Met Arg Glu Trp Val Ala Pro Glu Lys Ala Asp Ile Ile Val
                405                 410                 415

Ser Glu Leu Leu Gly Ser Phe Ala Asp Asn Glu Leu Ser Pro Glu Cys
            420                 425                 430

Leu Asp Gly Ala Gln His Phe Leu Lys Asp Asp Gly Val Ser Ile Pro
        435                 440                 445

Gly Glu Tyr Thr Ser Phe Leu Ala Pro Ile Ser Ser Ser Lys Leu Tyr
    450                 455                 460

Asn Glu Val Arg Ala Cys Arg Glu Lys Asp Arg Asp Pro Glu Ala Gln
465                 470                 475                 480

Phe Glu Met Pro Tyr Val Val Arg Leu His Asn Phe His Gln Leu Ser
                485                 490                 495

Ala Pro Gln Pro Cys Phe Thr Phe Ser His Pro Asn Arg Asp Pro Met
            500                 505                 510

Ile Asp Asn Asn Arg Tyr Cys Thr Leu Glu Phe Pro Val Glu Val Asn
        515                 520                 525

Thr Val Leu His Gly Phe Ala Gly Tyr Phe Glu Thr Val Leu Tyr Gln
    530                 535                 540

Asp Ile Thr Leu Ser Ile Arg Pro Glu Thr His Ser Pro Gly Met Phe
545                 550                 555                 560

Ser Trp Phe Pro Ile Leu Phe Pro Ile Lys Gln Pro Ile Thr Val Arg
                565                 570                 575

Glu Gly Gln Thr Ile Cys Val Arg Phe Trp Arg Cys Ser Asn Ser Lys
            580                 585                 590

Lys Val Trp Tyr Glu Trp Ala Val Thr Ala Pro Val Cys Ser Ala Ile
        595                 600                 605

His Asn Pro Thr Gly Arg Ser Tyr Thr Ile Gly Leu
    610                 615                 620


<210> SEQ ID NO 3
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

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<400> SEQUENCE: 5

Met His His His His His His
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<210> SEQ ID NO 6
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<213> ORGANISM: Artificial Sequence
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20 25 30

Glu Ile Ala Asp Thr Leu Gly Ala Val Ala Lys Gln Gly Phe Asp Phe
35 40 45

Leu Cys Met Pro Val Phe His Pro Arg Phe Lys Arg Glu Phe Ile Gln
50 55 60

Glu Pro Ala Lys Asn Arg Pro Gly Pro Gln Thr Arg Ser Asp Leu Leu
65 70 75 80

Leu Ser Gly Arg Asp Trp Asn Thr Leu Ile Val Gly Lys Leu Ser Pro
85 90 95

Trp Ile Arg Pro Asp Ser Lys Val Glu Lys Ile Arg Arg Asn Ser Glu
100 105 110

Ala Ala Met Leu Gln Glu Leu Asn Phe Gly Ala Tyr Leu Gly Leu Pro
115 120 125

Ala Phe Leu Leu Pro Leu Asn Gln Glu Asp Asn Thr Asn Leu Ala Arg
130 135 140

Val Leu Thr Asn His Ile His Thr Gly His His Ser Ser Met Phe Trp
145 150 155 160

Met Arg Val Pro Leu Val Ala Pro Glu Asp Leu Arg Asp Asp Ile Ile
165 170 175

Glu Asn Ala Pro Thr Thr His Thr Glu Glu Tyr Ser Gly Glu Glu Lys
180 185 190

Thr Trp Met Trp Trp His Asn Phe Arg Thr Leu Cys Asp Tyr Ser Lys
195 200 205

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Ile Ile Thr Gly Thr Asn His His Ser Glu Lys Glu Phe Cys Ser Tyr
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Leu Gln Tyr Leu Glu Tyr Leu Ser Gln Asn Arg Pro Pro Pro Asn Ala
    290                 295                 300

Tyr Glu Leu Phe Ala Lys Gly Tyr Glu Asp Tyr Leu Gln Ser Pro Leu
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Gln Pro Leu Met Asp Asn Leu Glu Ser Gln Thr Tyr Glu Val Phe Glu
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Lys Asp Pro Ile Lys Tyr Ser Gln Tyr Gln Gln Ala Ile Tyr Lys Cys
            340                 345                 350

Leu Leu Asp Arg Val Pro Glu Glu Glu Lys Asp Thr Asn Val Gln Val
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Leu Met Val Leu Gly Ala Gly Arg Gly Pro Leu Val Asn Ala Ser Leu
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Arg Ala Ala Lys Gln Ala Asp Arg Arg Ile Lys Leu Tyr Ala Val Glu
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Lys Asn Pro Asn Ala Val Val Thr Leu Glu Asn Trp Gln Phe Glu Glu
                405                 410                 415

Trp Gly Ser Gln Val Thr Val Val Ser Ser Asp Met Arg Glu Trp Val
            420                 425                 430

Ala Pro Glu Lys Ala Asp Ile Ile Val Ser Glu Leu Leu Gly Ser Phe
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Ala Asp Asn Glu Leu Ser Pro Glu Cys Leu Asp Gly Ala Gln His Phe
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Leu Lys Asp Asp Gly Val Ser Ile Pro Gly Glu Tyr Thr Ser Phe Leu
465                 470                 475                 480

Ala Pro Ile Ser Ser Ser Lys Leu Tyr Asn Glu Val Arg Ala Cys Arg
                485                 490                 495

Glu Lys Asp Arg Asp Pro Glu Ala Gln Phe Glu Met Pro Tyr Val Val
            500                 505                 510

Arg Leu His Asn Phe His Gln Leu Ser Ala Pro Gln Pro Cys Phe Thr
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Phe Ser His Pro Asn Arg Asp Pro Met Ile Asp Asn Asn Arg Tyr Cys
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Thr Leu Glu Phe Pro Val Glu Val Asn Thr Val Leu His Gly Phe Ala
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Gly Tyr Phe Glu Thr Val Leu Tyr Gln Asp Ile Thr Leu Ser Ile Arg
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Pro Glu Thr His Ser Pro Gly Met Phe Ser Trp Phe Pro Ile Leu Phe
            580                 585                 590

Pro Ile Lys Gln Pro Ile Thr Val Arg Glu Gly Gln Thr Ile Cys Val
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Arg Phe Trp Arg Cys Ser Asn Ser Lys Lys Val Trp Tyr Glu Trp Ala
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Tyr Thr Ile Gly Leu
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35 40 45

Leu Leu Gly Ala Ser Ser Leu Ser Gly Arg Cys Trp Ala Gly Ser Leu
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Trp Leu Phe Lys Asp Pro Cys Ala Ala Pro Asn Glu Gly Phe Cys Ser
65 70 75 80

Ala Gly Val Gln Thr Glu Ala Gly Val Ala Asp Leu Thr Trp Val Gly
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Glu Arg Gly Ile Leu Val Ala Ser Asp Ser Gly Ala Val Glu Leu Trp
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Glu Leu Asp Glu Asn Glu Thr Leu Ile Val Ser Lys Phe Cys Lys Tyr
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Glu His Asp Asp Ile Val Ser Thr Val Ser Val Leu Ser Ser Gly Thr
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Gln Ala Val Ser Gly Ser Lys Asp Ile Cys Ile Lys Val Trp Asp Leu
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Ala Gln Gln Val Val Leu Ser Ser Tyr Arg Ala His Ala Ala Gln Val
165 170 175

Thr Cys Val Ala Ala Ser Pro His Lys Asp Ser Val Phe Leu Ser Cys
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Ser Glu Asp Asn Arg Ile Leu Leu Trp Asp Thr Arg Cys Pro Lys Pro
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Ala Ser Gln Ile Gly Cys Ser Ala Pro Gly Tyr Leu Pro Thr Ser Leu
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Ala Trp His Pro Gln Gln Ser Glu Val Phe Val Phe Gly Asp Glu Asn
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Gly Thr Val Ser Leu Val Asp Thr Lys Ser Thr Ser Cys Val Leu Ser
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Ser Ala Val His Ser Gln Cys Val Thr Gly Leu Val Phe Ser Pro His
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Ser Val Pro Phe Leu Ala Ser Leu Ser Glu Asp Cys Ser Leu Ala Val
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Leu Asp Ser Ser Leu Ser Glu Leu Phe Arg Ser Gln Ala His Arg Asp
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Phe Val Arg Asp Ala Thr Trp Ser Pro Leu Asn His Ser Leu Leu Thr
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Thr Val Gly Trp Asp His Gln Val Val His His Val Val Pro Thr Glu
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Pro Leu Pro Ala Pro Gly Pro Ala Ser Val Thr Glu
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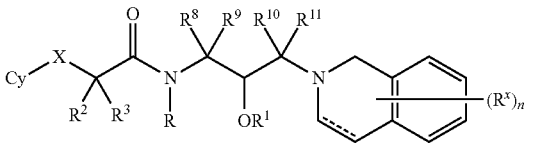
What is claimed is:

1. A compound of Formula (I):



I

or a pharmaceutically acceptable salt thereof,

wherein:

------ represents a single or double bond;

R^1 is hydrogen, R^z, or —C(O)R^z, wherein R^z is optionally substituted C_{1-6} alkyl;

X is a bond, —O—, —N(R)—, —CR^4R^5—, —O—CR^4R^5, —N(R)—CR^4R^5—, —O—CR^4R^5—O—, —N(R)—CR^4R^5—O, —N(R)—CR^4R^5—N(R)—, —O—CR^4R^5—N(R)—, —CR^4R^5—O—, —CR^4R^5—N(R)—, —O—CR^4R^5—CR^6R^7—, —N(R)—CR^4R^5—CR^6R^7—, —CR^6R^7—CR^4R^5—O—, —CR^6R^7—CR^4R^5—N(R)—, or —CR^6R^7—CR^4R^5—;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

R^2 and R^3 are independently selected from the group consisting of hydrogen, halo, —CN, —NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)_2$, —SR^A, —C(=O)R^A, —C(O)OR^A, —C(O)SR^A, —C(O)$N(R^B)_2$, —C(O)$N(R^B)N(R^B)_2$, —OC(O)R^A, —OC(O)$N(R^B)_2$, —NR^BC(O)R^A, —NR^BC(O)$N(R^B)_2$, —NR^BC(O)$N(R^B)N(R^B)_2$, —NR^BC(O)OR^A, —SC(O)R^A, —C(=NR^B)R^A, —C(=NNR^B)R^A, —C(=NOR^A)R^A, —C(=NR^B)$N(R^B)_2$, —NR^BC(=NR^B)R^B, —C(=S)R^A, —C(=S)$N(R^B)_2$, —NR^BC(=S)R^A, —S(O)R^A, —$OS(O)_2R^A$, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$; or R^2 and R^3 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

R^4 and R^5 are independently selected from the group consisting of hydrogen, halo, —CN, —NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)_2$, —SR^A, —C(=O)R^A, —C(O)OR^A, —C(O)SR^A, —C(O)$N(R^B)_2$, —C(O)$N(R^B)N(R^B)_2$, —OC(O)R^A, —OC(O)$N(R^B)_2$, —NR^BC(O)R^A, —NR^BC(O)$N(R^B)_2$, —NR^BC(O)$N(R^B)N(R^B)_2$, —NR^BC(O)OR^A, —SC(O)R^A, —C(=NR^B)R^A, —C(=NNR^B)R^A, —C(=NOR^A)R^A, —C(=NR^B)$N(R^B)_2$, —NR^BC(=NR^B)R^B, —C(=S)R^A, —C(=S)$N(R^B)_2$, —NR^BC(=S)R^A, —S(O)R^A, —$OS(O)_2R^A$, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$; or R^4 and R^5 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

R^6 and R^7 are independently selected from the group consisting of hydrogen, halo, —CN, —NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)_2$, —SR^A, —C(=O)R^A, —C(O)OR^A, —C(O)SR^A, —C(O)$N(R^B)_2$, —C(O)$N(R^B)N(R^B)_2$, —OC(O)R^A, —OC(O)$N(R^B)_2$, —NR^BC(O)R^A, —NR^BC(O)$N(R^B)_2$, —NR^BC(O)$N(R^B)N(R^B)_2$, —NR^BC(O)OR^A, —SC(O)R^A, —C(=NR^B)R^A, —C(=NNR^B)R^A, —C(=NOR^A)R^A, —C(=NR^B)$N(R^B)_2$, —NR^BC(=NR^B)R^B, —C(=S)R^A, —C(=S)$N(R^B)_2$, —NR^BC(=S)R^A, —S(O)R^A, —$OS(O)_2R^A$, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$; or R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

R^8, R^9, R^{10}, and R^{11} are independently hydrogen, halo, or optionally substituted aliphatic;

Cy is a monocyclic or bicyclic carbocyclic group or a monocyclic or bicyclic aryl group, substituted with 0, 1, 2, 3, or 4 R^v groups;

each R^v is independently selected from the group consisting of halo, —CN, —NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, —OR^A, —$N(R^B)_2$, —SR^A, —C(=O)R^A, —C(O)OR^A, —C(O)SR^A, —C(O)$N(R^B)_2$, —C(O)$N(R^B)N(R^B)_2$, —OC(O)R^A, —OC(O)$N(R^B)_2$, —NR^BC(O)R^A, —NR^BC(O)$N(R^B)_2$, —NR^BC(O)$N(R^B)N(R^B)_2$, —NR^BC(O)OR^A, —SC(O)R^A, —C(=NR^B)R^A, —C(=NNR^B)R^A, —C(=NOR^A)R^A, —C(=NR^B)$N(R^B)_2$, —NR^BC(=NR^B)R^B, —C(=S)R^A, —C(=S)$N(R^B)_2$, —NR^BC(=S)R^A, —S(O)R^A, —$OS(O)_2R^A$, —SO_2R^A, —$NR^BSO_2R^A$, and —$SO_2N(R^B)_2$; or an R^v group may be optionally taken together with R^2 or R^3 to form an optionally substituted 5- to 6-membered carbocyclic or heterocyclic ring fused to Cy;

each R^x is independently selected from the group consisting of halo, —CN, optionally substituted aliphatic, —OR', and —N(R")$_2$;

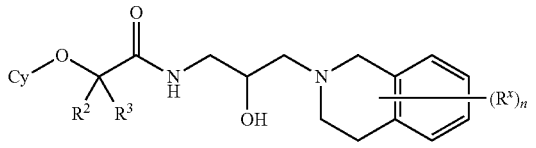
R' is hydrogen or optionally substituted aliphatic;

each R" is independently hydrogen or optionally substituted aliphatic, or two R" are taken together with their intervening atoms to form an optionally substituted heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits;

wherein each instance of aliphatic is independently an alkyl, alkenyl, alkynyl, cycloalkyl, or cycloalkenyl group.

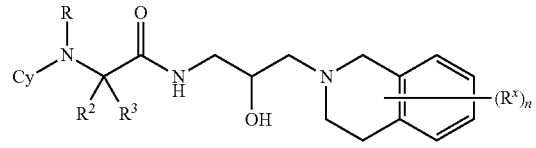
2. The compound of claim 1, wherein the compound is of Formula (II):



II

or a pharmaceutically acceptable salt thereof.

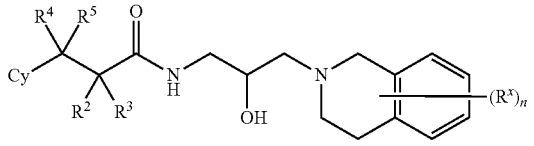
3. The compound of claim 1, wherein the compound is of Formula (III):



III

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, wherein the compound is of Formula (IV):



IV

or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, wherein R^1 is hydrogen.

6. The compound of claim 1, wherein n is 0, 1, or 2.

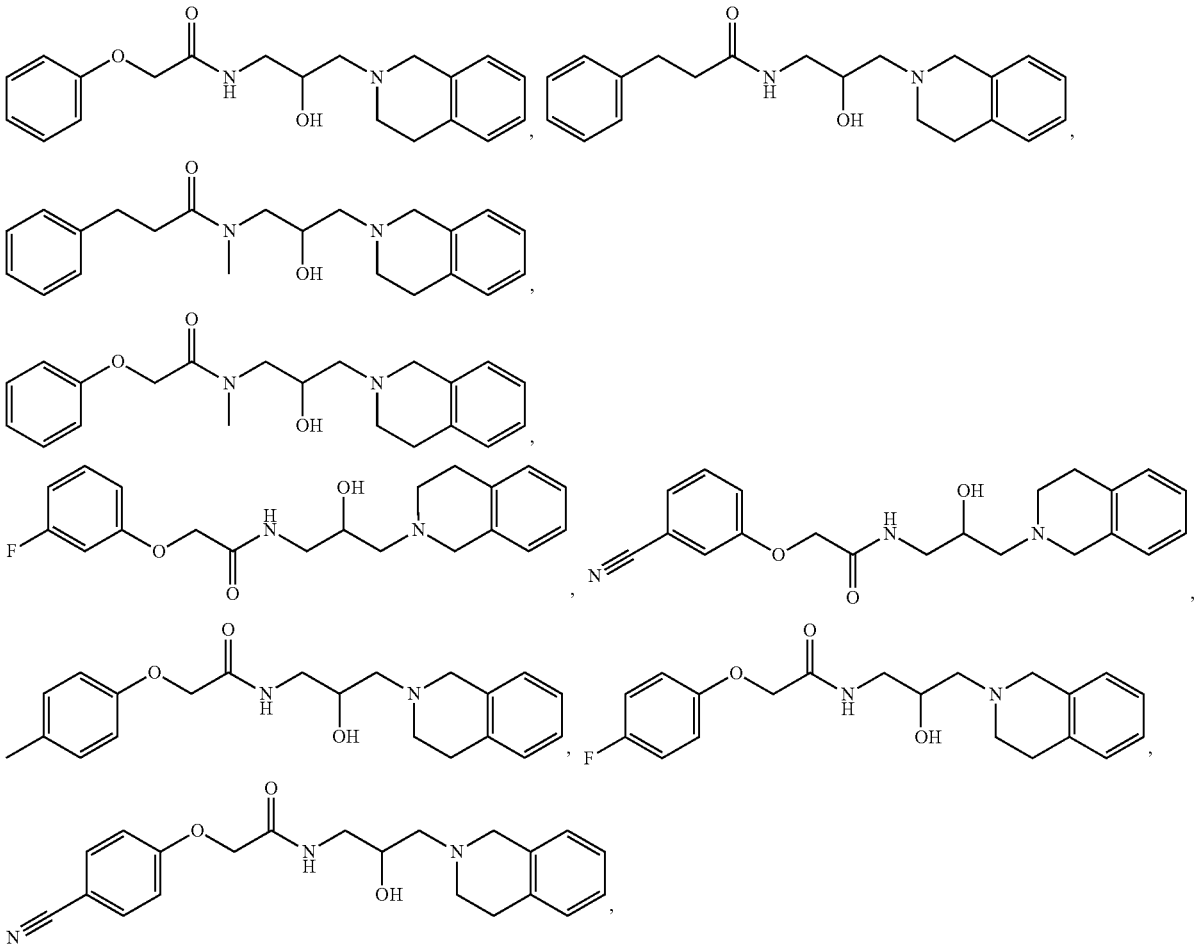
7. The compound of claim 1, wherein R^2 is hydrogen.

8. The compound of claim 1, wherein R is hydrogen.

9. The compound of claim 1, wherein Cy is phenyl substituted with 0, 1, 2, 3, or 4 R^y groups.

10. The compound of claim 1, wherein Cy is a bicyclic carbocyclic group or a bicyclic aryl group, substituted with 0, 1, 2, 3, or 4 R^y groups.

11. The compound of claim 1, wherein the compound is selected from the group consisting of:



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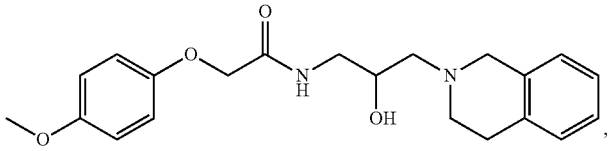

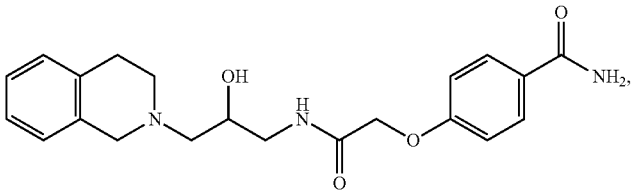

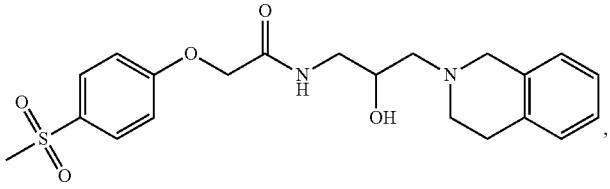

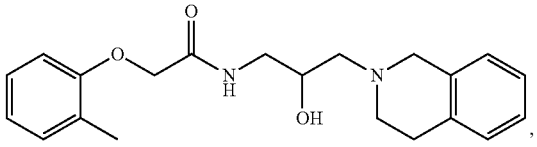

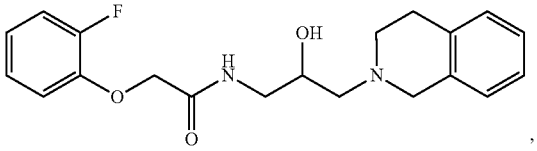

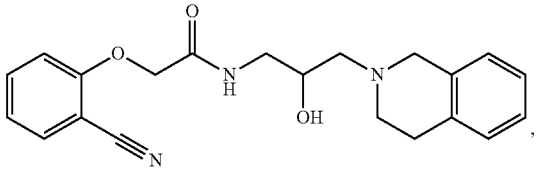

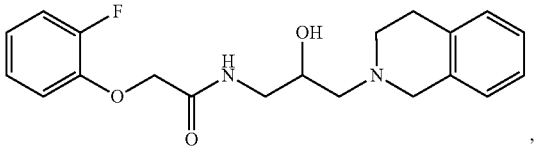

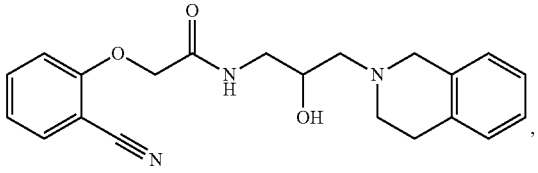

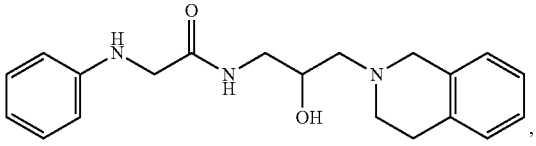

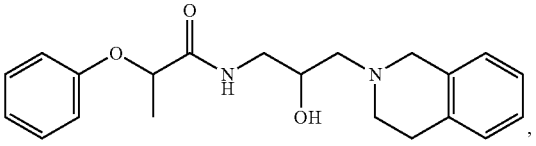

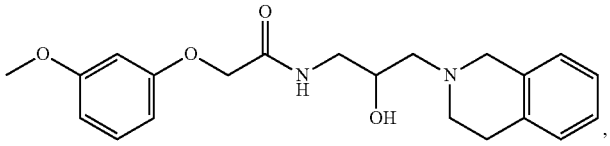

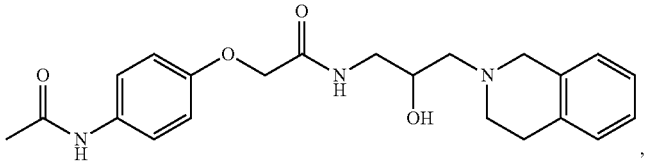

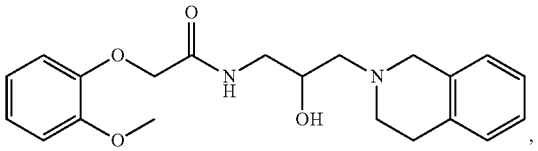

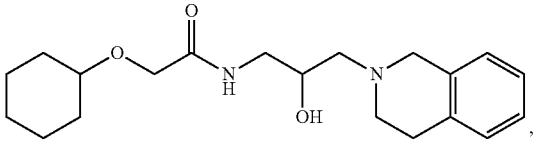

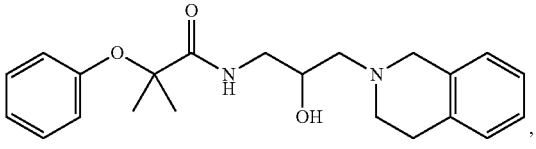

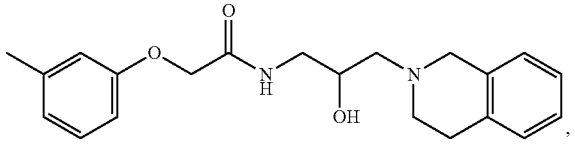

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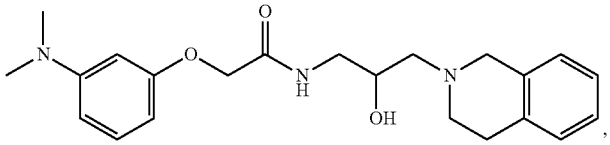

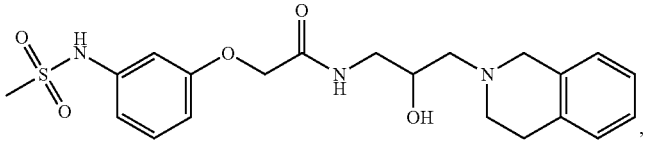

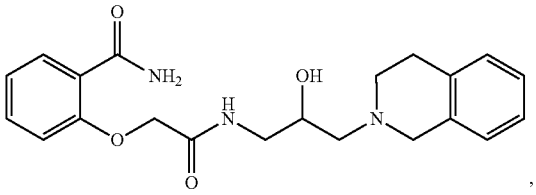

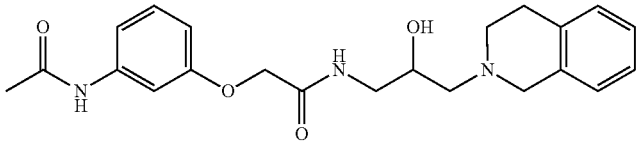

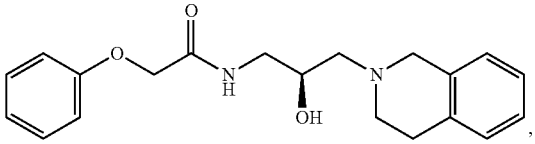

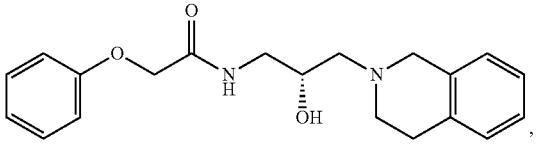

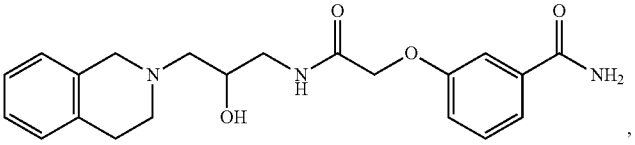

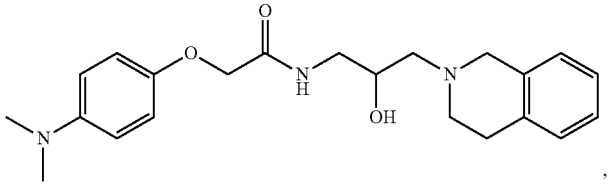

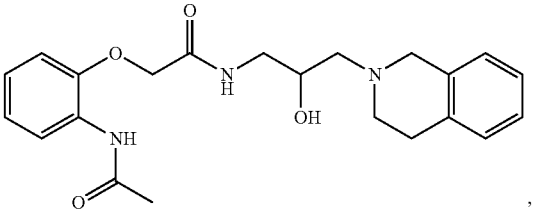

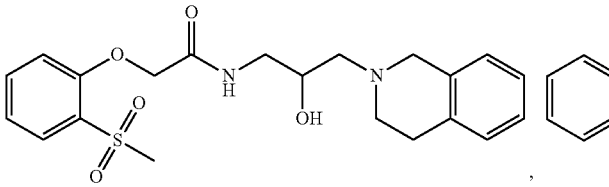

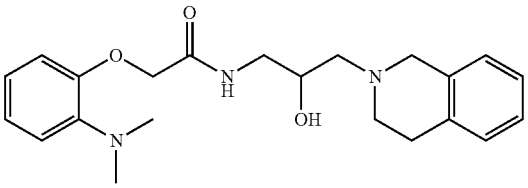

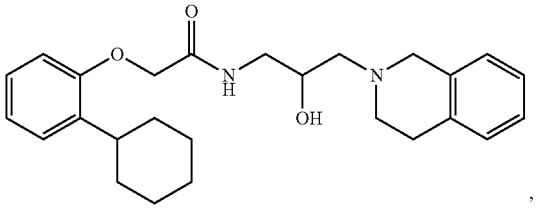

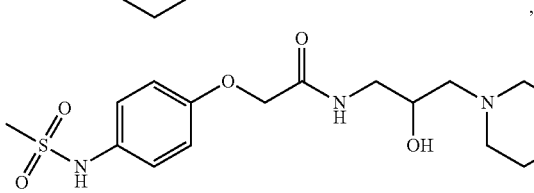

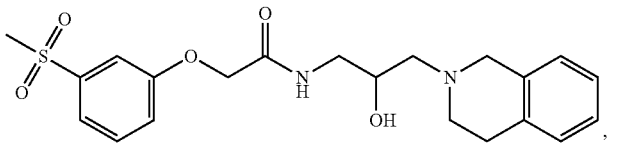

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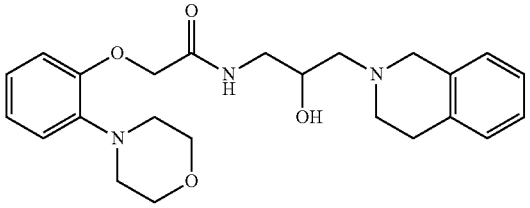

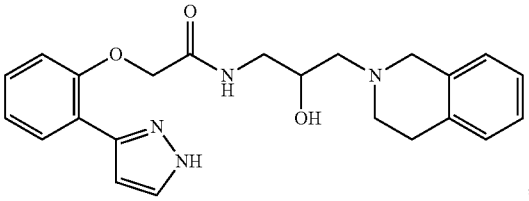

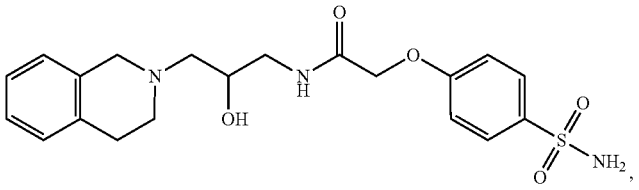

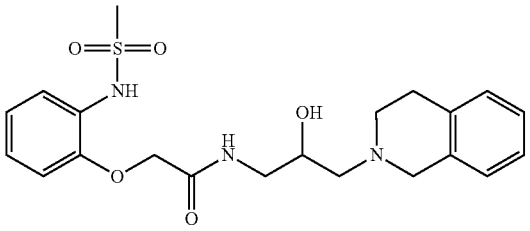

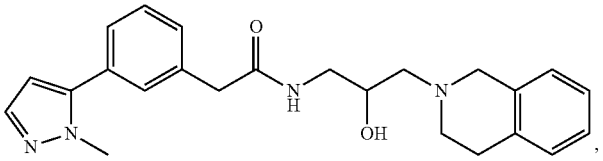

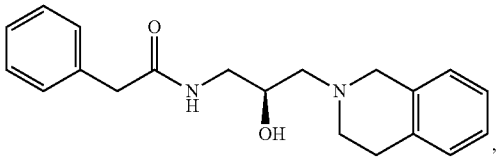

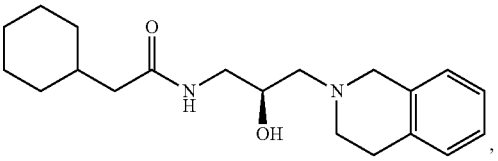

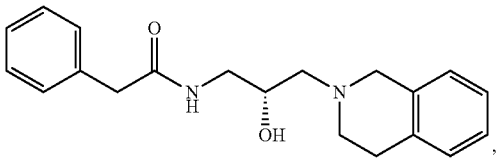

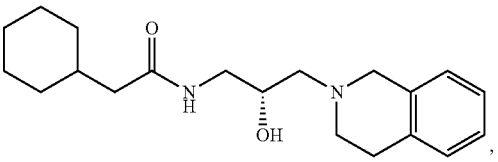

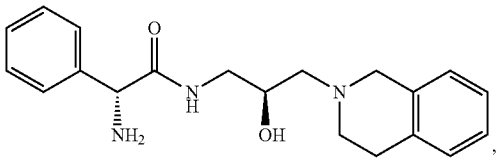

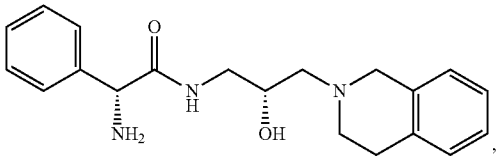

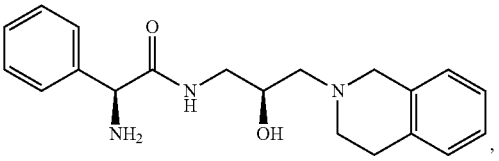

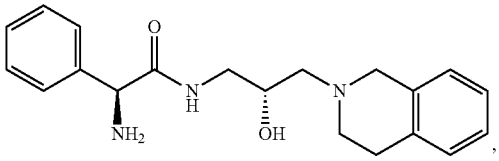

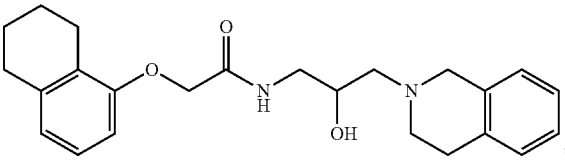

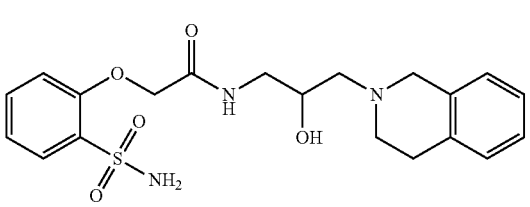

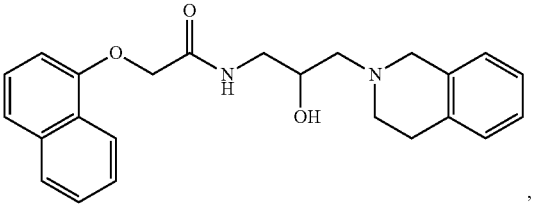

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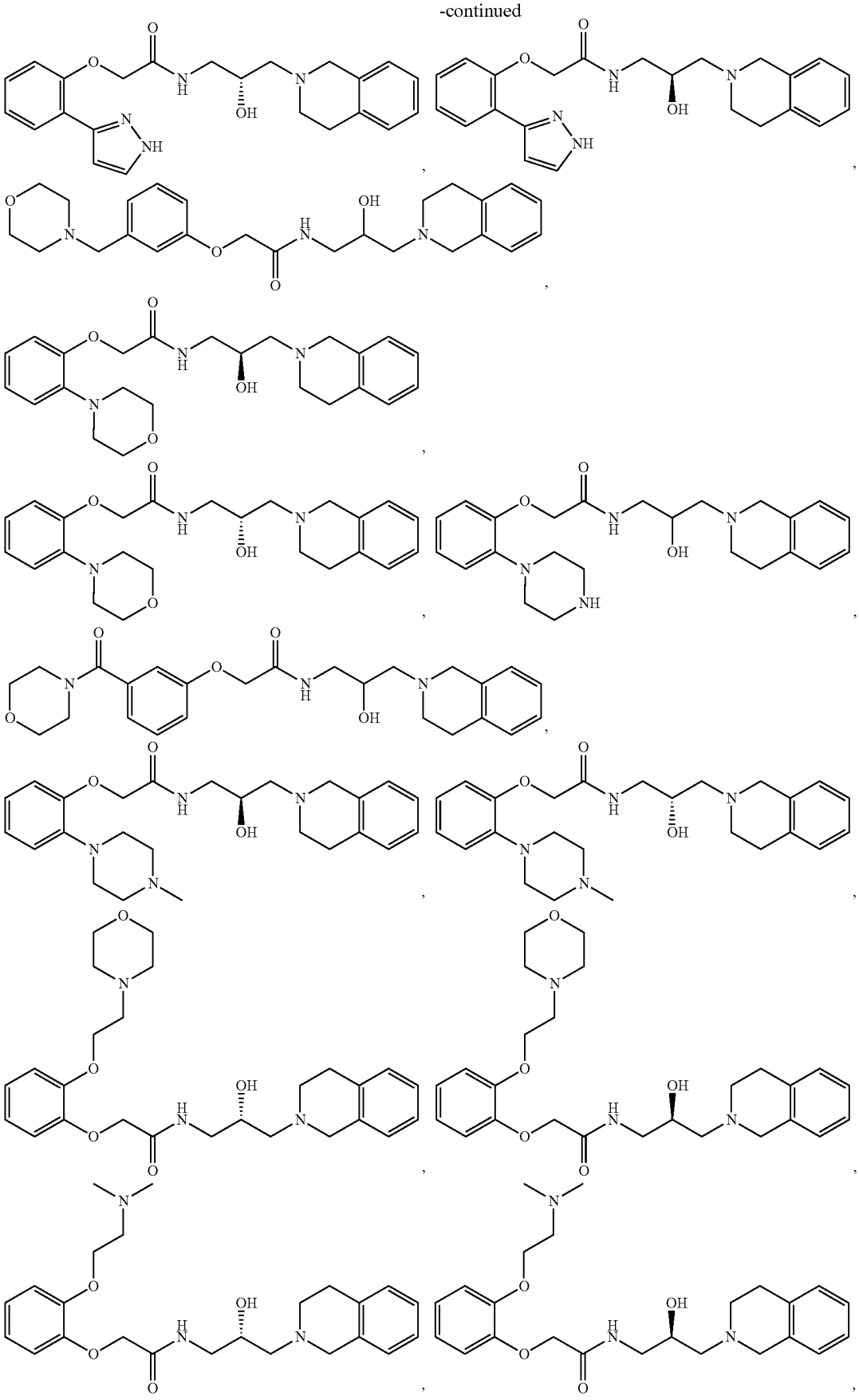

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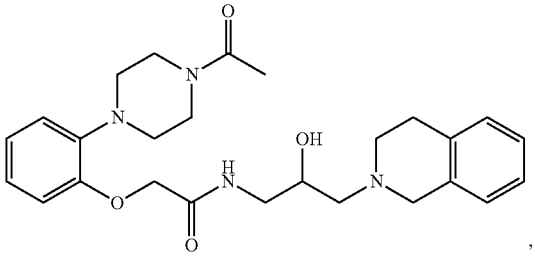

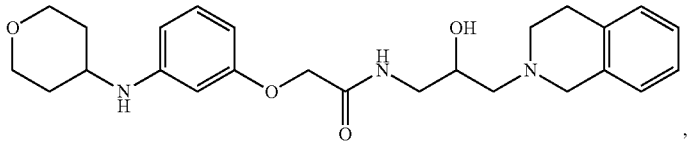

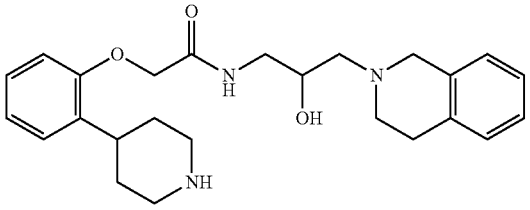

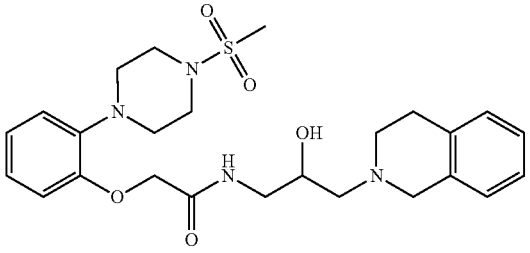

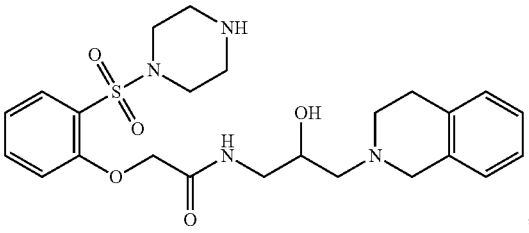

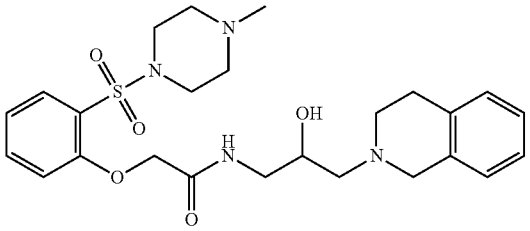

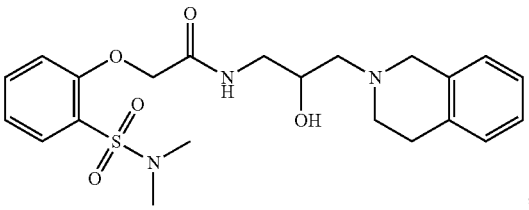

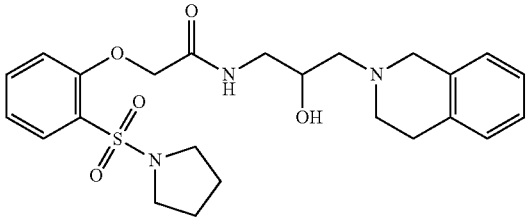

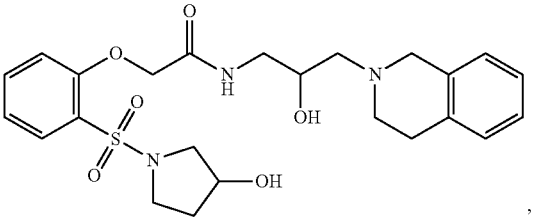

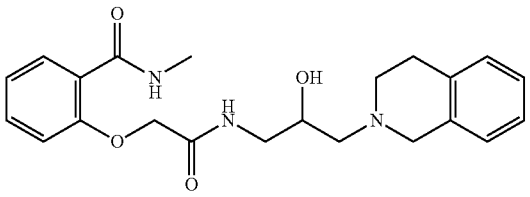

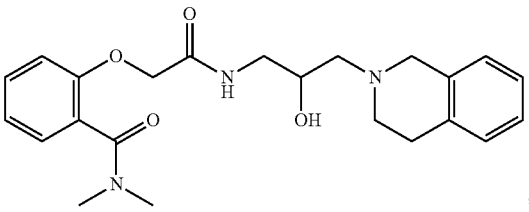

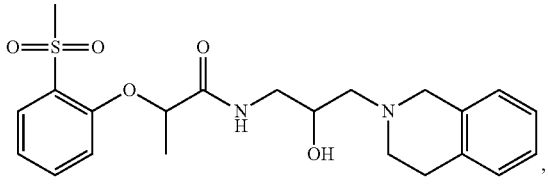

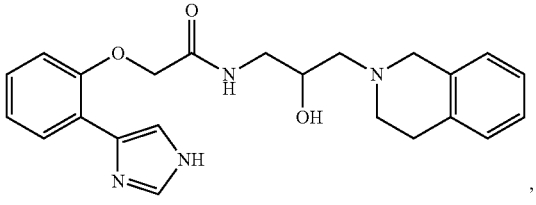

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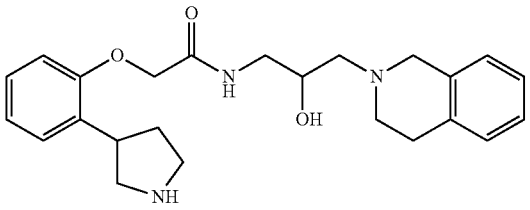

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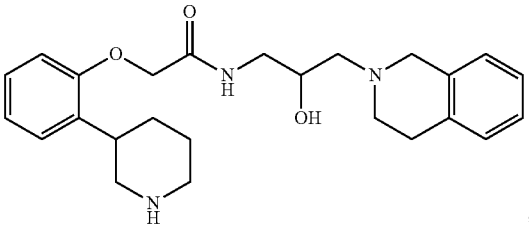

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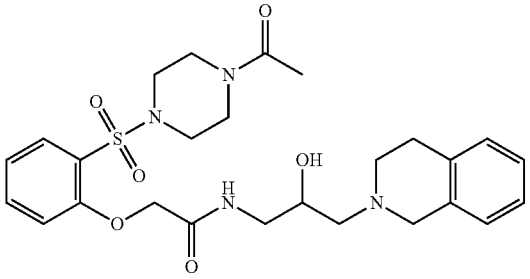

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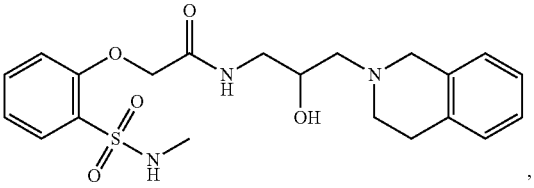

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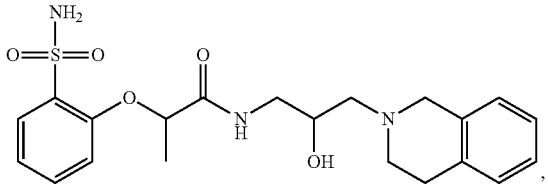

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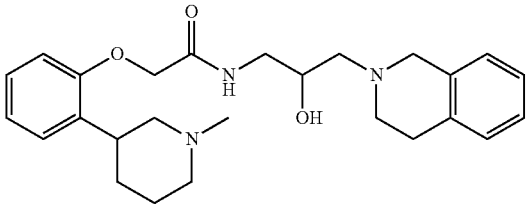

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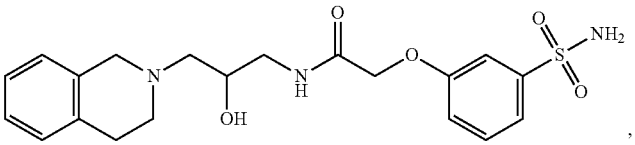

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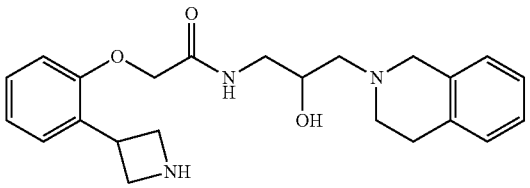

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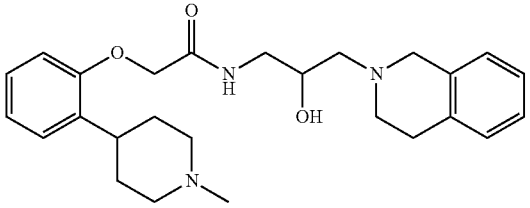

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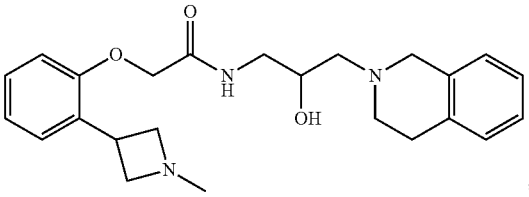

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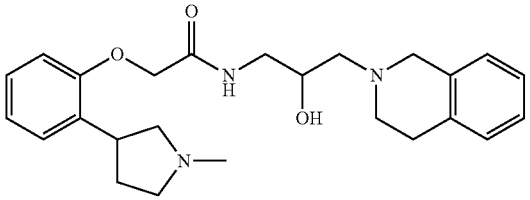

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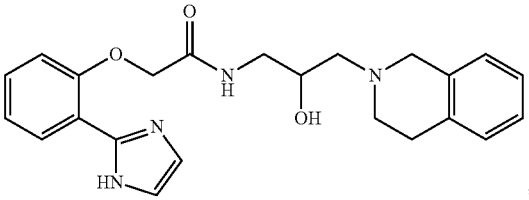

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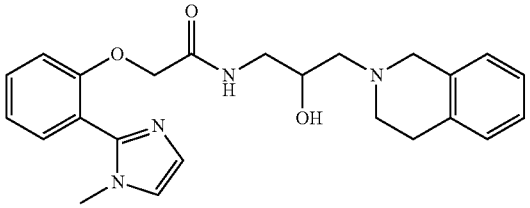

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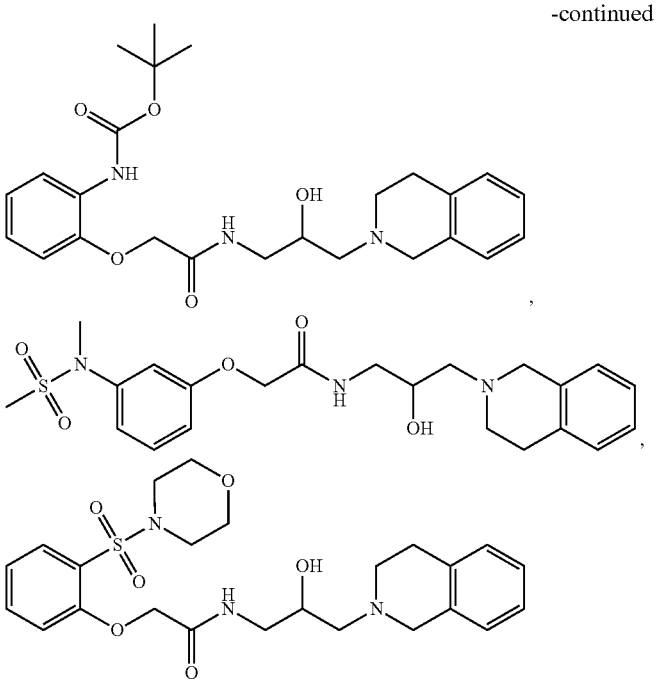


and pharmaceutically acceptable salts thereof.

12. A pharmaceutical composition comprising a compound of claim **1** or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

13. A method of treating a PRMT5-mediated disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim **1** or a pharmaceutically acceptable salt thereof;

wherein the PRMT5-mediated disorder is cancer, a metabolic disorder, or a hemoglobinopathy;

wherein the cancer is a hematopoietic cancer, lung cancer, prostate cancer, melanoma, or pancreatic cancer; and

wherein the metabolic disorder is diabetes or obesity.

14. The method of claim **13**, wherein the PRMT5-mediated disorder is cancer, and wherein the cancer is a hematopoietic cancer, lung cancer, prostate cancer, melanoma, or pancreatic cancer.

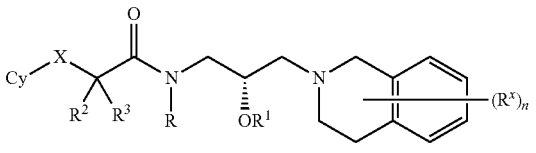
15. The method of claim **13**, wherein the PRMT5-mediated disorder is a metabolic disorder, and wherein the metabolic disorder is diabetes or obesity.

16. The method of claim **13**, wherein the PRMT5-mediated disorder is a hemoglobinopathy.

17. The method of claim **16**, wherein the hemoglobinopathy is sickle cell anemia or β-thalessemia.

18. The compound of claim **1**, wherein the compound is of Formula (I'-a):

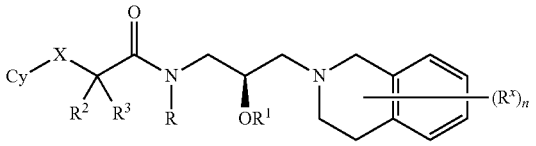
(I'-a)



or a pharmaceutically acceptable salt thereof.

19. The compound of claim **1**, wherein the compound is of Formula (I'-b):

(I'-b)

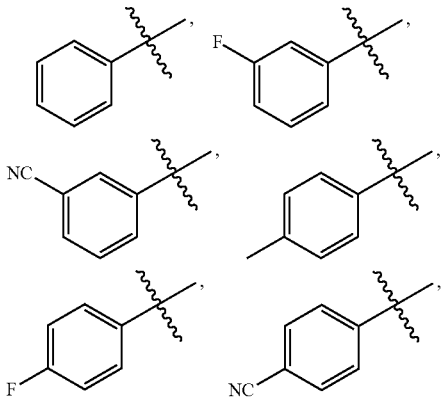


or a pharmaceutically acceptable salt thereof.

20. The compound of claim **1**, wherein R^2 and R^3 are each hydrogen.

21. The compound of claim **1**, wherein each of R^8, R^9, R^{10}, and R^{11} are hydrogen.

22. The compound of claim **1**, wherein Cy is selected from the group consisting of:



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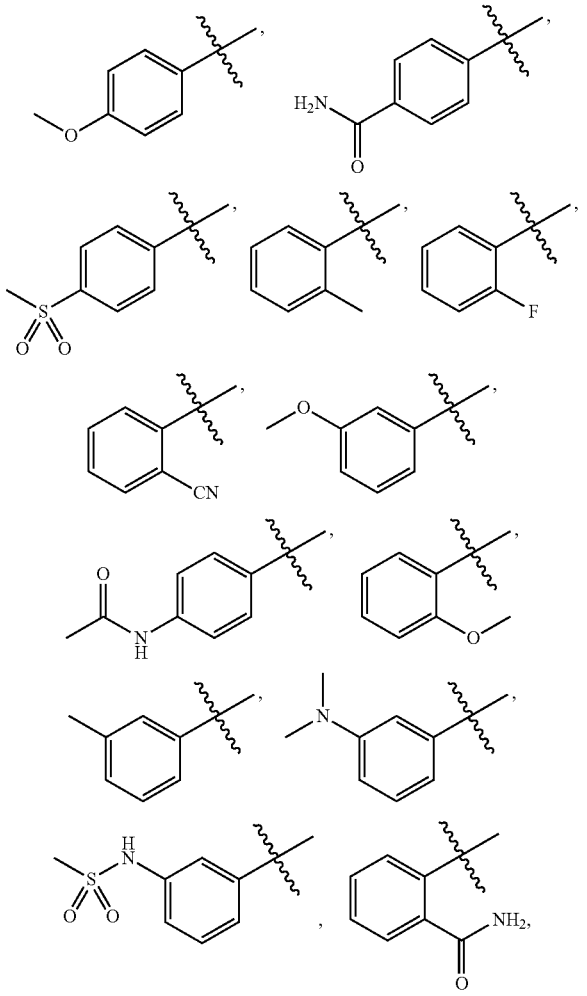

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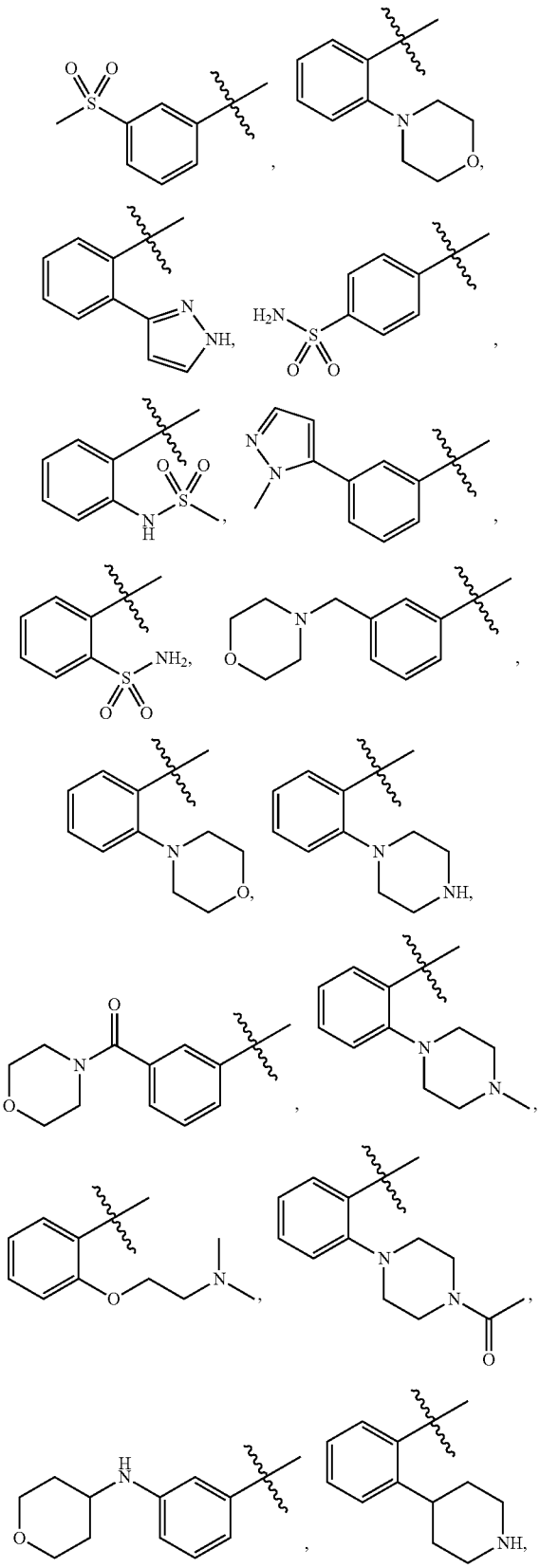

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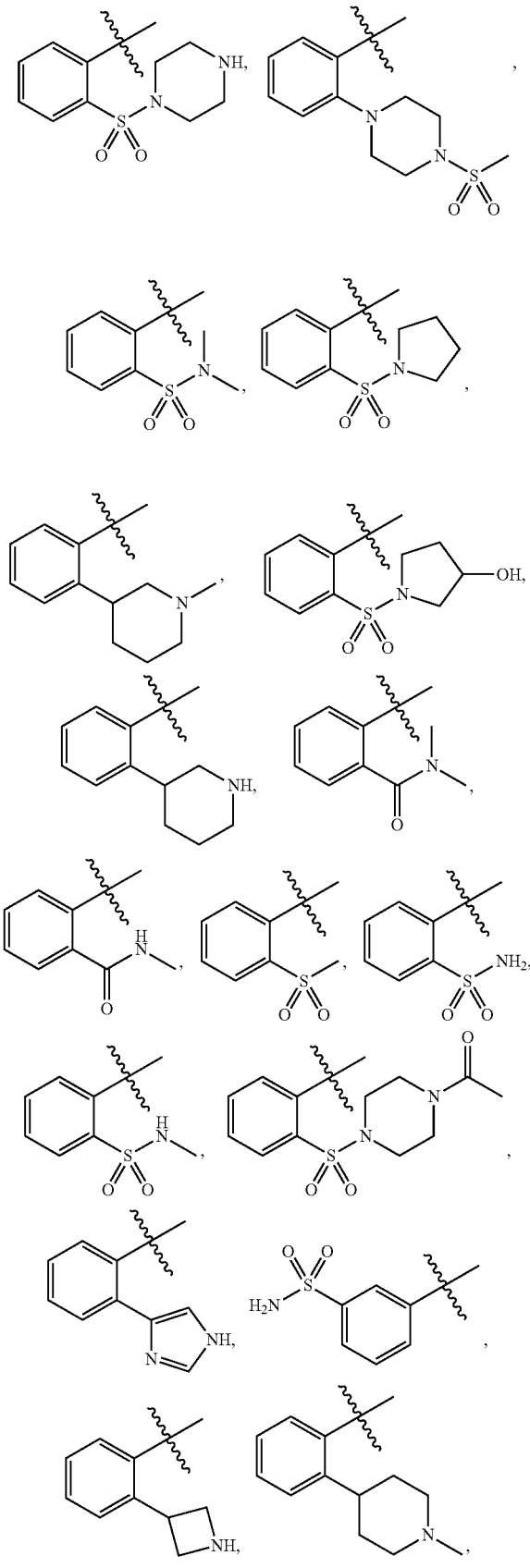

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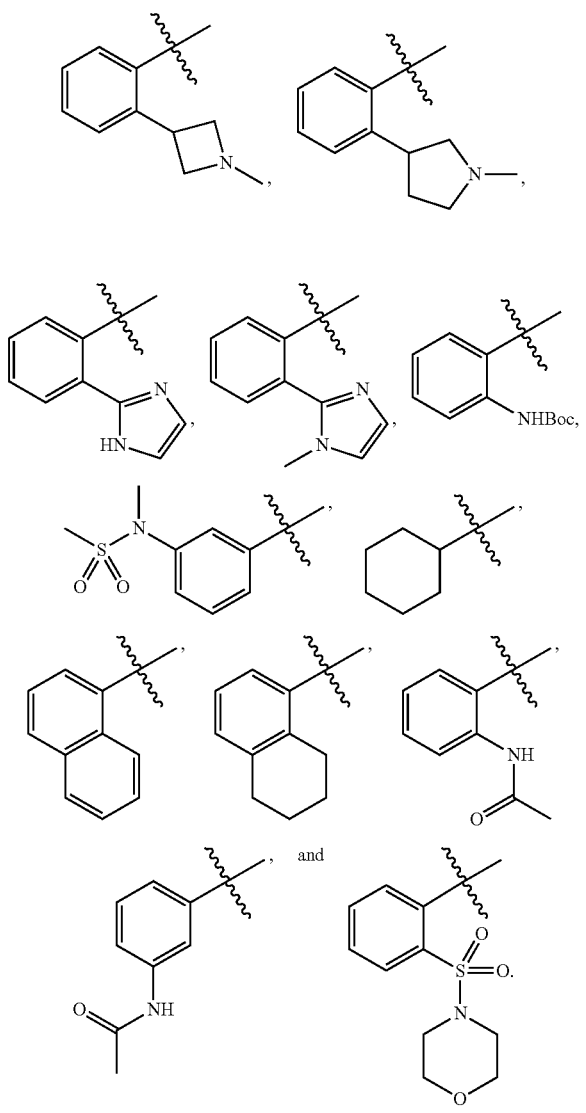
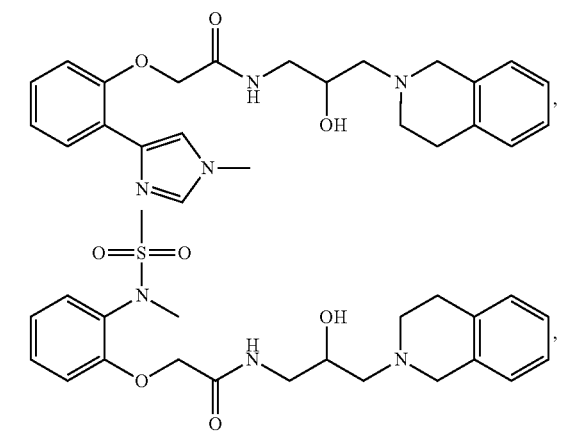


and

23. The compound of claim **1**, wherein the compound is selected from the group consisting of:



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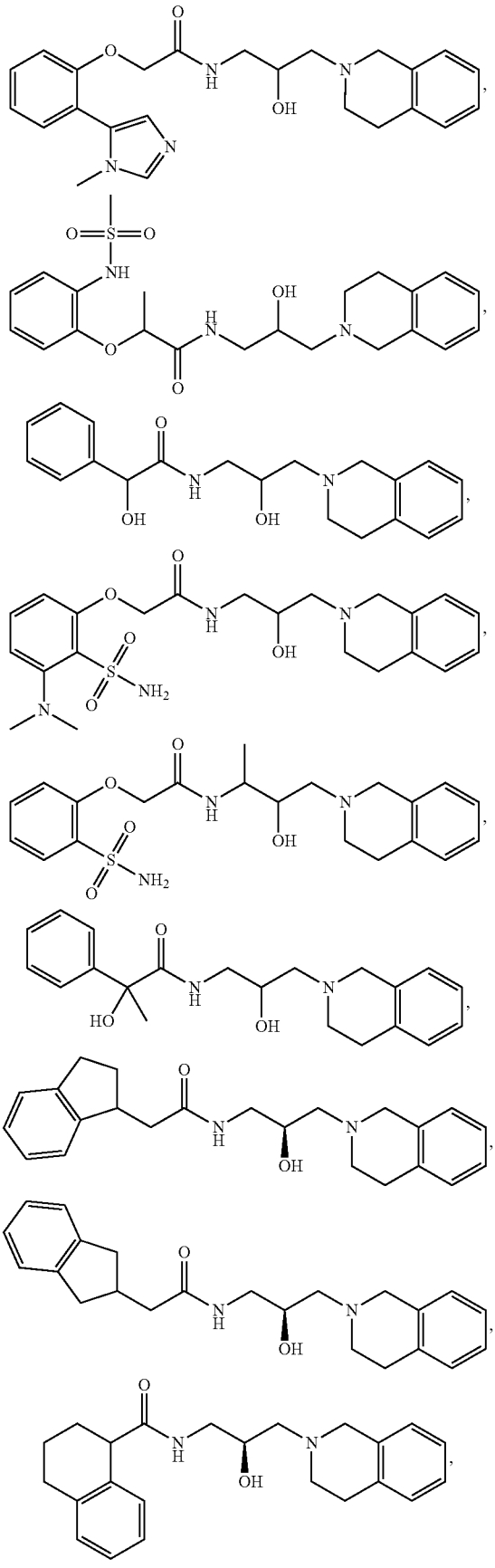

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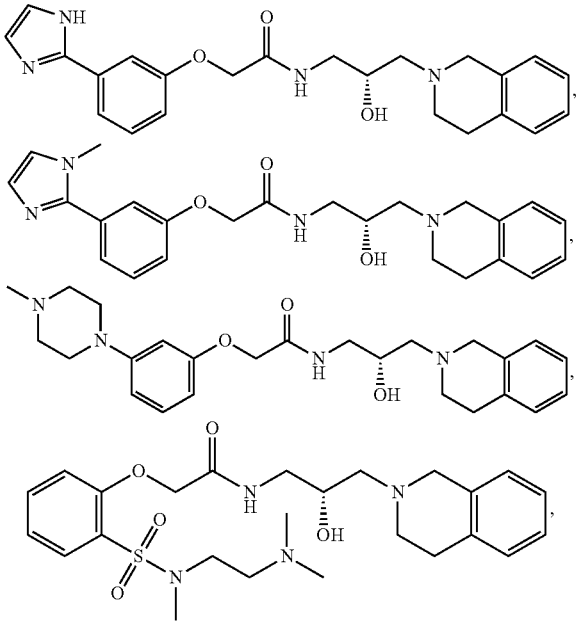
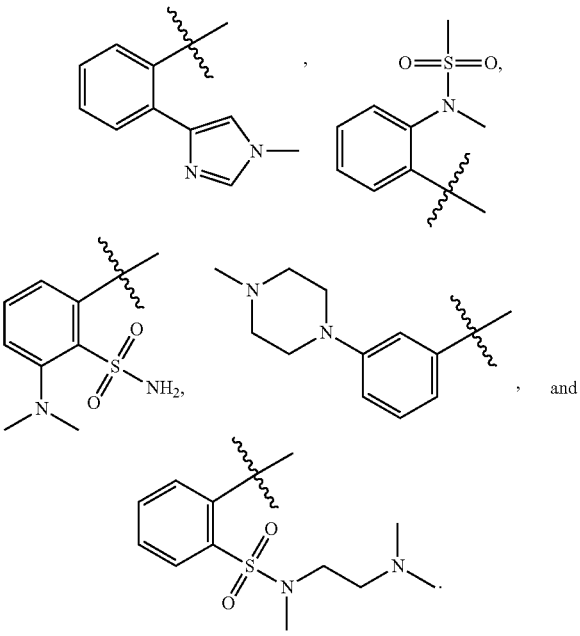
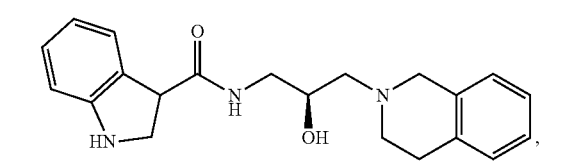


and pharmaceutically acceptable salts thereof.

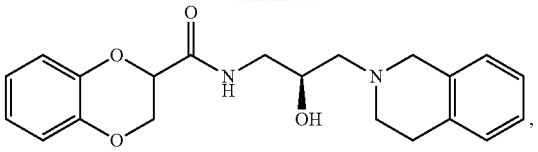
24. The compound of claim **1**, wherein Cy is selected from the group consisting of:

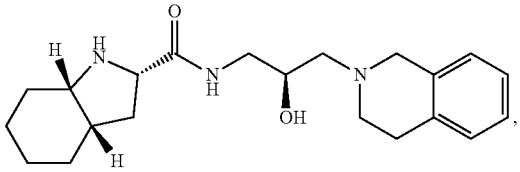


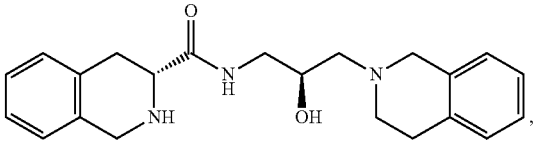
25. The compound of claim **1**, wherein the compound is selected from the group consisting of:



-continued







and pharmaceutically acceptable salts thereof.

26. A pharmaceutical composition comprising a compound of claim **11** or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

27. A pharmaceutical composition comprising a compound of claim **23** or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

28. A pharmaceutical composition comprising a compound of claim **25** or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

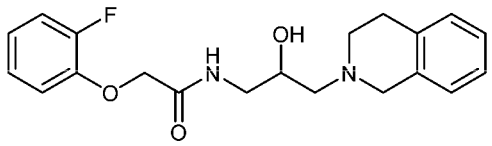
CERTIFICATE OF CORRECTION

PATENT NO. : 9,266,836 B2
APPLICATION NO. : 14/561538
DATED : February 23, 2016
INVENTOR(S) : Kenneth W. Duncan et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

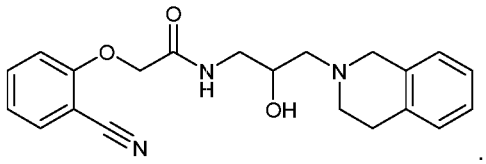
In the Claims

In claim 11, the 5th compound listed in column 203 is a duplicate of the preceding 4th compound listed in column 203. Please remove the second occurrence of the compound of formula:



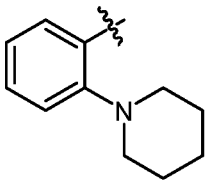
.

In claim 11, the 3rd compound listed in column 204 is a duplicate of the preceding 2nd compound listed in column 204. Please remove the second occurrence of the compound of formula:

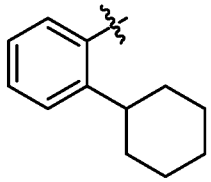


.

In claim 22, column 217, lines 60-65, the formula:



should be:



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Signed and Sealed this
Ninth Day of August, 2016

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office